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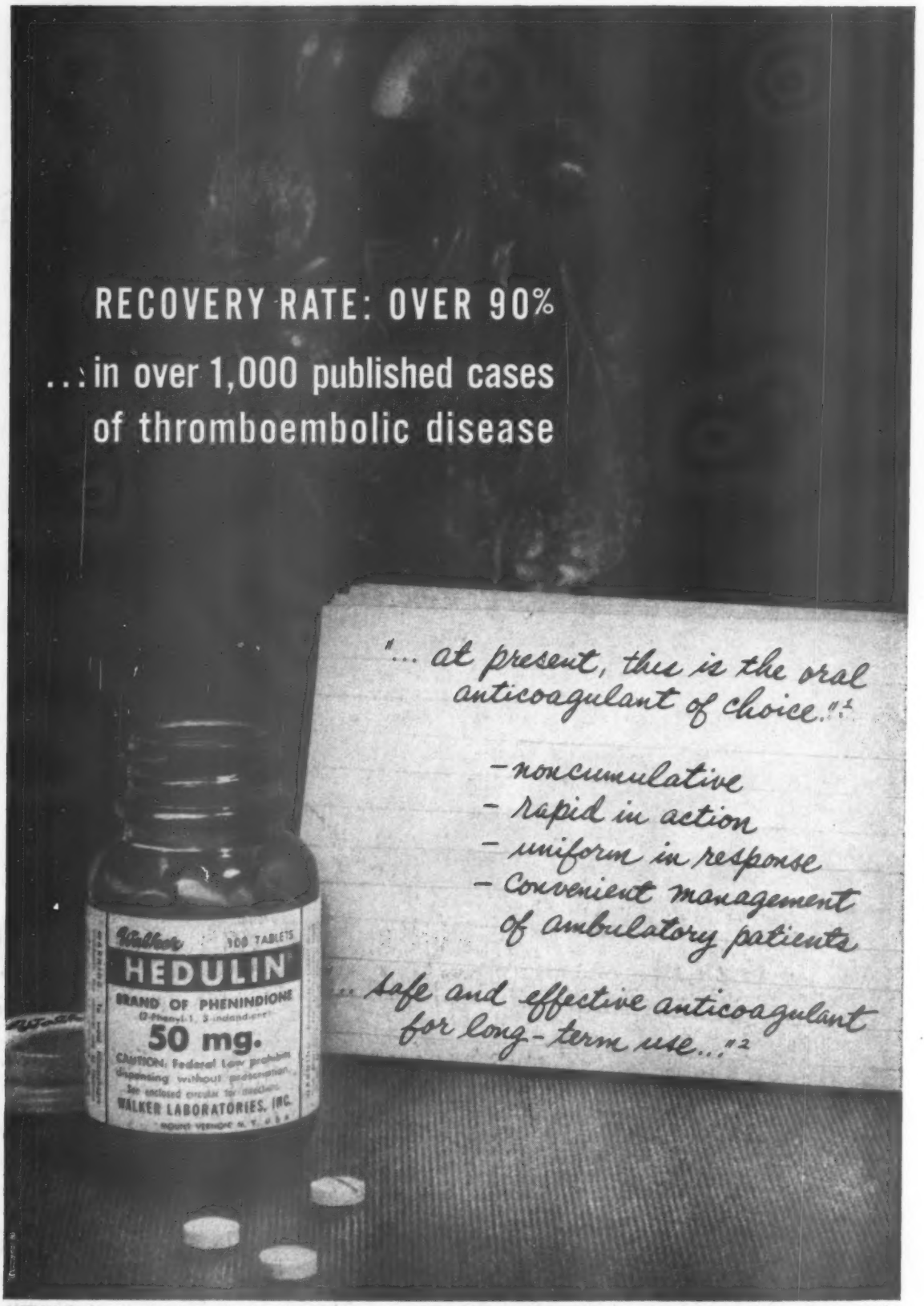
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Symposium on Persistent Atrioventricular Canal

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1. Breneman, G. M., and Priest, E. McC.: Am. Heart J. 50:129 (July) 1955. 2. Tandowsky, R. M.: Am. J. Cardiol. 3:551 (April) 1959.

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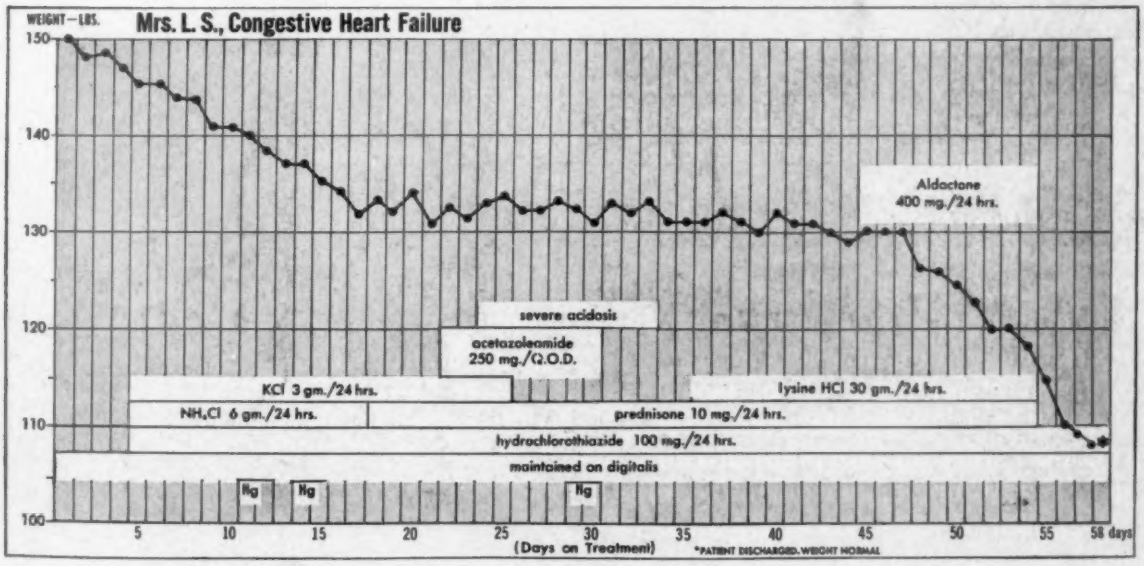
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References: **1.** Tandowsky, R. M.: Personal communication. **2.** Parsons, W. B.: *Curr. Therapeut. Res.* 2:137 (May) 1960. **3.** Thompson, C. E.: Personal communication. **4.** Biben, L. H.; Kurstin, W., and Protas, M.: Personal communication. **5.** Hobbs, T. G.: Personal communication.

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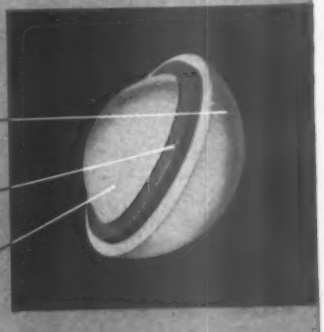
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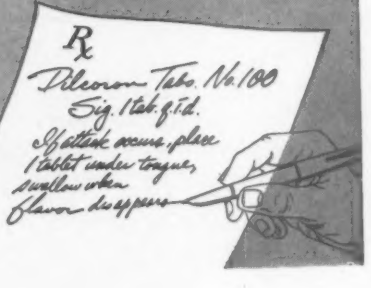


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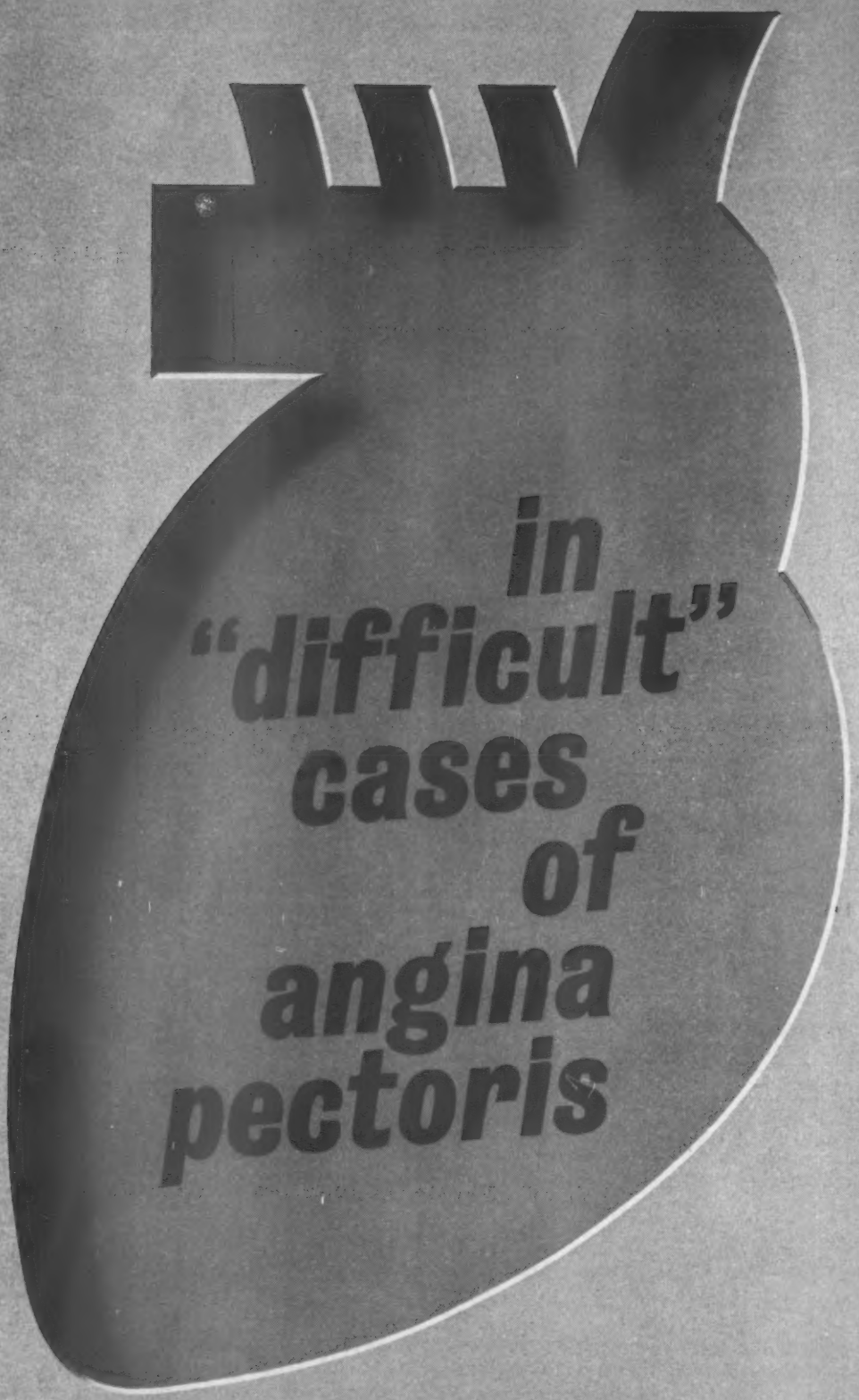
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☐ *J. M. Yoffey*—**QUANTITATIVE CELLULAR HEMATOLOGY.** *Pub. '60, 144 pp., 17 il., (2 in full color), (Amer. Lec. Hematology).*

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ENCOURAGING NEWS IN ANGINAL THERAPY

Reporting on extensive clinical trial of ISORDIL, a group of important investigators found "impressive improvement in 67% of patients...,"[1] favorable response in a total of 75%.

1. Fisch, S., Boyle, A., Sperber, R., and DeGraff, A. C.

In their thoroughly documented report on 60 angina patients studied by open clinical trial, Fisch, Boyle, Sperber, and DeGraff found improvement in 75% of patients; 18% did not respond. Minor side reactions (mostly headache) hindered evaluation in only 7% of the patients treated.

Average Dosage Low, but Individualization Required

Average effective dose of ISORDIL was 10 mg. q.i.d.; 26% of patients received higher doses, 16% lower doses. Of all patients, 87% received and tolerated 5 to 15 mg. q.i.d.

Headache Commonest Side Effect, Easily Relieved

Although headache occurred initially in 27% of patients studied, it caused discontinuance of ISORDIL in only 4 patients. Continued therapy, adjustment of dosage, or use of acetylsalicylic acid relieved headache in all other cases.

Other Studies Confirm Results, Establish Additional Benefits

Maintenance of active coronary vasodilatation by ISORDIL, as shown by Leslie,[2] Albert[3] and Fremont,[4] virtually eliminates periods of unprotection. Benefits are apparent as early as 15 minutes, persist for at least 4 hours. No lag in onset . . . important during early morning and postprandial stress.

References: 1. Fisch, S., Boyle, A., Sperber, R., and DeGraff, A.C.: Presented at the annual meeting of the American Therapeutic Society, Miami Beach, Florida, June 10, 1960. To be published. 2. Leslie, R.: Submitted for publication. 3. Albert, A.: In Manuscript. 4. Fremont, R.E.: To be published.

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Nitroglycerin is the drug of choice for the **ACUTE ATTACK**

'CARDILATE'

may well be chosen for **PROLONGED PROPHYLAXIS**

CLINICAL OPINION

"... the magnitude of the response to 15 mg. ['Cardilate'] was comparable to that following nitroglycerin.... The comparatively prolonged duration of action of erythrol tetranitrate when given sublingually makes it especially valuable for clinical use."[1]

CLINICAL OPINION

"Nitroglycerin and erythrol tetranitrate when administered sublingually are among the most potent of all prophylactic agents available for the treatment of patients with angina pectoris."[2]

CLINICAL OPINION

"Erythrol tetranitrate exhibits an inherent long-acting vasodilating effect. Therefore it is the drug of choice in angina pectoris."[3]

'CARDILATE' brand
Erythrol Tetranitrate Sublingual Tablets

NEW

5 mg., scored 

15 mg., scored 

Bottles of 100 tablets.

Complete literature available on request.

1. Riseman, J.E.F., *et al.*: Circulation *17*:22 (Jan.) 1958.

2. Russek, H.I.: Circulation *18*:774 (Oct.) 1958.

3. Hirshleifer, I., *et al.*: Scientific Exhibit, A.M.A., Atlantic City, N. J., June, 1959.



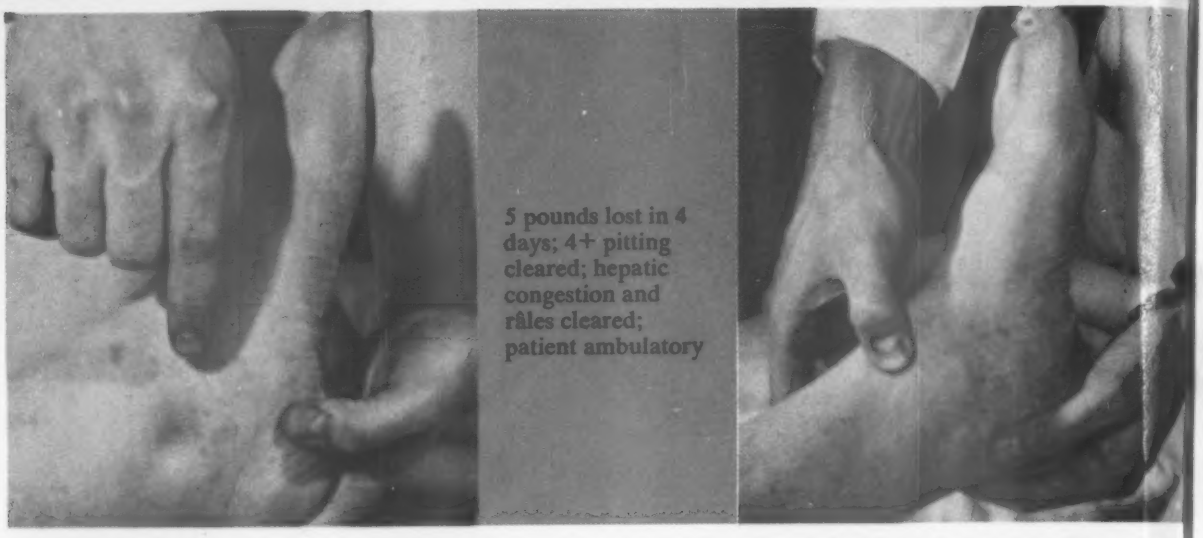
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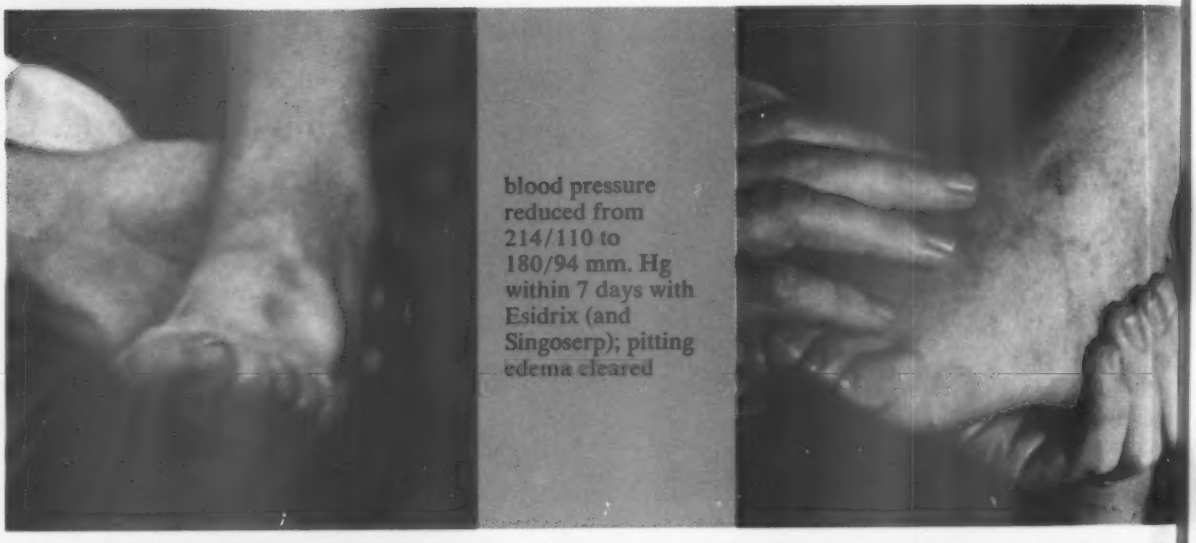


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hospitalized patient with congestive heart failure

5 pounds lost in 4 days; 4+ pitting cleared; hepatic congestion and râles cleared; patient ambulatory



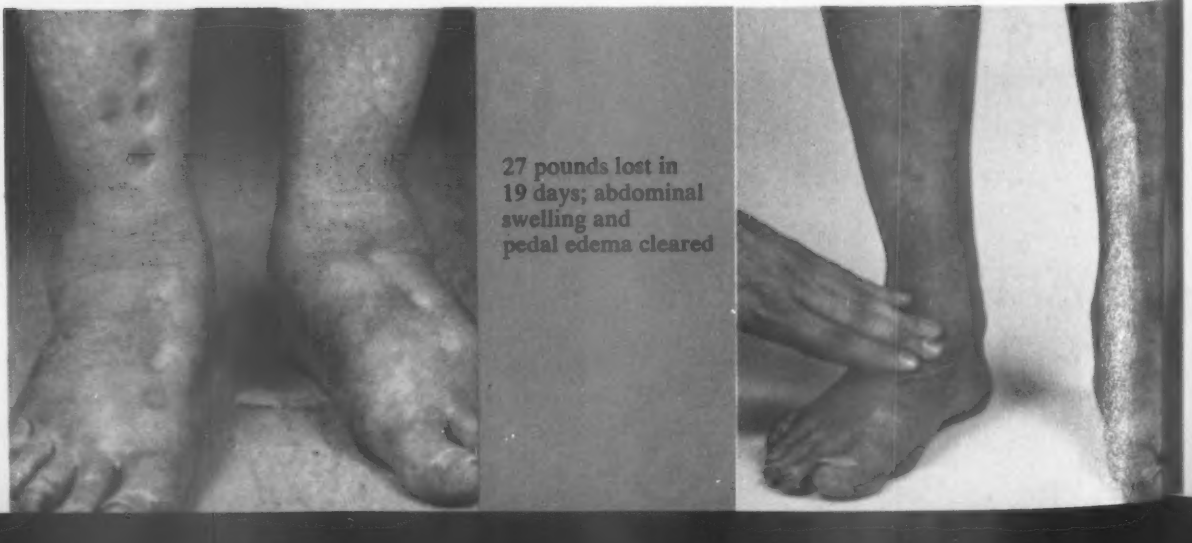
office patient treated for pedal edema and persistently high diastolic pressure

blood pressure reduced from 214/110 to 180/94 mm. Hg within 7 days with Esidrix (and Singoserp); pitting edema cleared



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27 pounds lost in 19 days; abdominal swelling and pedal edema cleared

Photos used with permission of the patients

marked benefits in patient after patient with edema and hypertension plus built-in potassium protection

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- Three tablets supply 75 mg. Esidrix plus potassium equivalent to a quart of fresh orange juice. ESIDRIX-K is coated to prevent gastric irritation.
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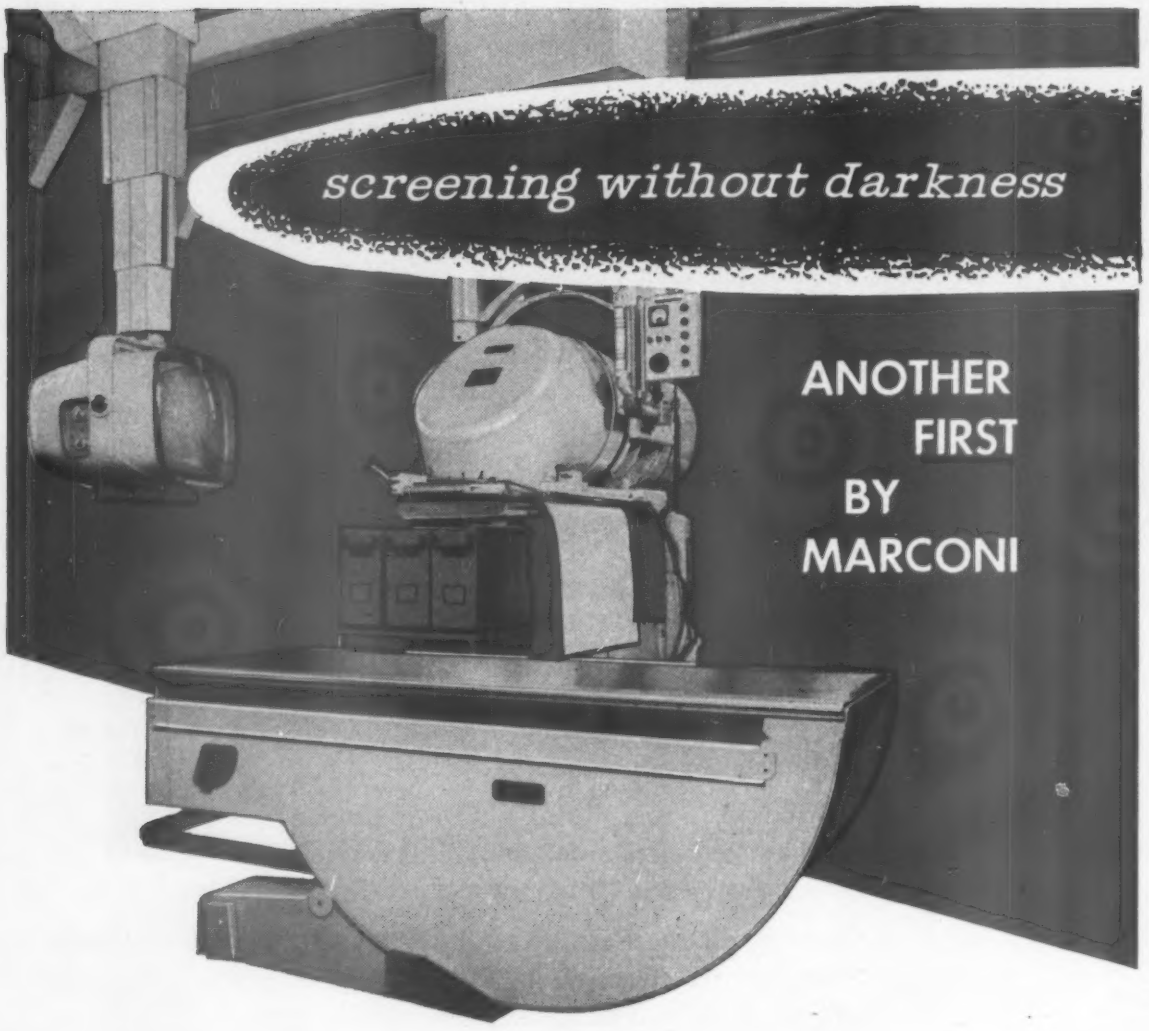
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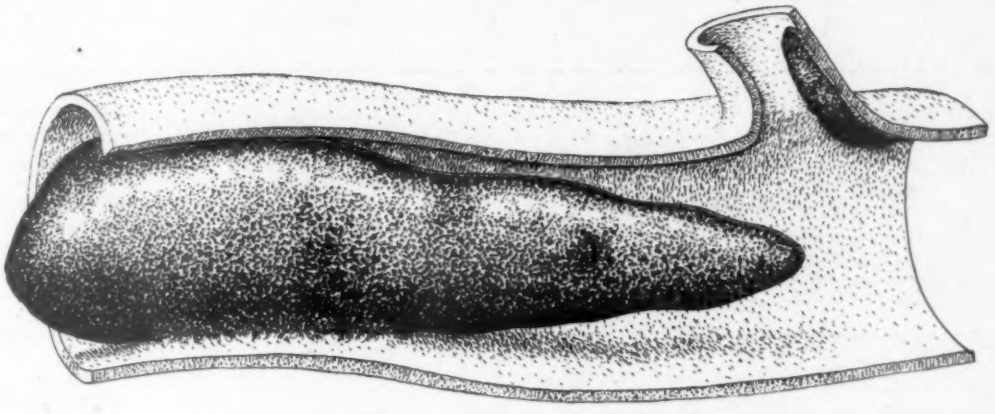
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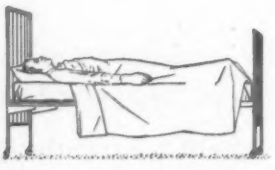
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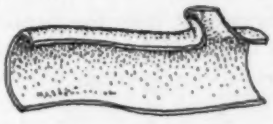
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FIBRINOLYSIN, HUMAN

early use greatly reduces morbidity and mortality in thrombophlebitis, phlebothrombosis, pulmonary embolism, and certain arterial thrombi

Results of therapy	Bed rest
Effect on intravascular thrombi	 Clot may form permanent obstruction to blood flow. New clots may form.
Effect on pulmonary emboli	 Sudden death from pulmonary embolism is an ever-present hazard. One or more nonfatal pulmonary emboli may result in irreversible lung damage or secondary pneumonia.
Effect on duration of illness and convalescence	 Weeks of hospitalization or bed rest at home are commonly required in the management of thrombophlebitis, phlebothrombosis, pulmonary embolism, and arterial thrombosis.
Frequency and severity of postphlebitic syndrome	 Chronic leg swelling, severe secondary varicose veins, and leg ulcers are common sequelae.



Anticoagulant + Bed rest		THROMBOLYSIN + Anticoagulant + Bed rest	
	Anticoagulants cannot remove formed clot. However, they help prevent its extension and minimize formation of new clots.		Recently formed intravascular clots are lysed and the formation of new clots is inhibited. Circulation is restored and maintained, with rapid symptomatic relief.
	The careful use of anticoagulants reduces the occurrence of pulmonary emboli.		The incidence and severity of pulmonary emboli are greatly reduced since THROMBOLYSIN acts to remove thrombi before they can become emboli.
	Thromboembolic illness and convalescence are shortened.		A striking reduction is observed in the duration of hospital stay, bed rest, and convalescence.
	The incidence and severity of the postphlebitic syndrome are reduced.		Postphlebitic complications are prevented or greatly minimized.



What is THROMBOLYSIN?

THROMBOLYSIN is Fibrinolysin, Human. It is prepared by activating the profibrinolysin-rich Fraction III – 3 of pooled human plasma with highly-purified streptokinase and then lyophilizing it. THROMBOLYSIN helps restore the natural equilibrium between clot formation and clot lysis, thereby enhancing the ability of the blood to maintain normal flow.

In What Conditions is it Indicated?

THROMBOLYSIN is indicated in thrombophlebitis, phlebothrombosis, pulmonary embolism, and certain arterial thrombi.

*(NOTE: *Successful lysis of thrombi of major cerebral vessels has been reported. However, additional experience is required to define the indications and contraindications of therapy in such patients. THROMBOLYSIN has also been administered to patients with acute myocardial infarction, but the scope of this work is still too limited to permit conclusions about its safety or benefit.*)

When Should Therapy be Initiated?

Treatment with THROMBOLYSIN should be started as soon as possible after a thrombus has formed. Blood clots begin to organize shortly after formation and may become encased in a layer of endothelial cells, making them resistant to the action of THROMBOLYSIN. Usually, more rapid lysis can be expected to take place when treatment is initiated within five days after a thrombus has formed; however, in some cases successful lysis has been accomplished when treatment was not initiated for several weeks after thrombus formation.

Can THROMBOLYSIN be Given to Patients Being Treated with Anticoagulants?

Yes. Patients who have been on anticoagulant therapy can be expected to improve when THROMBOLYSIN is added to their program of treatment.

Does THROMBOLYSIN Increase the Incidence of Embolism?

Clinical studies indicate that it does not. In fact, if any evidence of embolization should appear, it is important to continue THROMBOLYSIN until symptoms have disappeared.

What is the Dosage?

The dosage most frequently used by investigators has been 4 vials (200,000 MSD units) per day by intravenous infusion. This is usually administered by giving 1 vial per hour for 4 consecutive hours. Alternatively, 1 vial (50,000 MSD units) per hour may be given for 2 consecutive hours and repeated in 3 to 6 hours. The dosage range is 1 vial (50,000 MSD units) to 2 vials (100,000 MSD units) an hour by intravenous drip, for 1 to 6 hours, depending on the nature of the clot and the response

Vascular thrombi
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treated rapidly
by a new agent

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of the patient. Most patients respond in one day; those who do not may require additional doses for three or four successive days.

Patients not under active treatment with anticoagulants at the time of the thromboembolic episode:

New clot formation is unlikely to occur during the administration of THROMBOLYSIN, so that anticoagulants may be unnecessary in this period. However, the fibrinolytic activity of THROMBOLYSIN persists only 3 to 4 hours after cessation of infusion; in patients subject to thrombosis, provision should be made to provide adequate therapeutic anticoagulant effect at this time.

Patients under active treatment with anticoagulants:

Within recommended dosages, THROMBOLYSIN produces only minor alterations in the clotting mechanism: the prothrombin time is generally increased by only a few seconds, the Lee-White clotting time by only 1 to 4 minutes, and the fibrinogen levels generally decrease by about 30 percent of control values. In themselves, these alterations are probably of no clinical significance. In patients on concurrent anticoagulant therapy in whom the clotting mechanism is depressed to midtherapeutic levels, the small additional depression due to THROMBOLYSIN should produce no added danger; however, the addition of THROMBOLYSIN may be hazardous when the therapeutic anticoagulant level already threatens to exceed safe limits.

What Other Precautions are Necessary?

THROMBOLYSIN is contraindicated in the presence of a hemorrhagic diathesis or hypofibrinogenemia. Fibrinolytic activity usually increases spontaneously for a short period after anesthesia or surgery. Therefore, THROMBOLYSIN should be used with caution because lysis of the clots at the operative site may occur.

Bleeding from open wounds or recent operative sites can occur during therapy. Usually this has been observed only in patients receiving both an anticoagulant and THROMBOLYSIN. In such cases, the bleeding was controlled by the use of plasma or whole blood transfusions. A specific antagonist to the anticoagulant may also be used.

What Side Effects May Occur?

Febrile reactions may occur, but these are rarely severe. When they do occur, the temperature usually rises rapidly to a peak, then returns to normal within 24 hours. In some patients, a rise in temperature above 1.5 to 2 degrees F. is accompanied by chills, nausea, vomiting, dizziness, headache, muscle pain, back pain, tachycardia, or hypotension.

How is it Supplied? 100-cc. vials containing 50,000 MSD units.

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New Rautrax-N results in prompt lowering of blood pressure.[1] Rautrax-N, a new and carefully developed antihypertensive-diuretic preparation, provides improved therapeutic action[1] plus enhanced diuretic safety for all degrees of essential hypertension. A combination of Raudixin and Naturetin, Rautrax-N facilitates the management of hypertension when rauwolfia alone proves inadequate, or when prolonged treatment, with or without associated edema, is indicated.

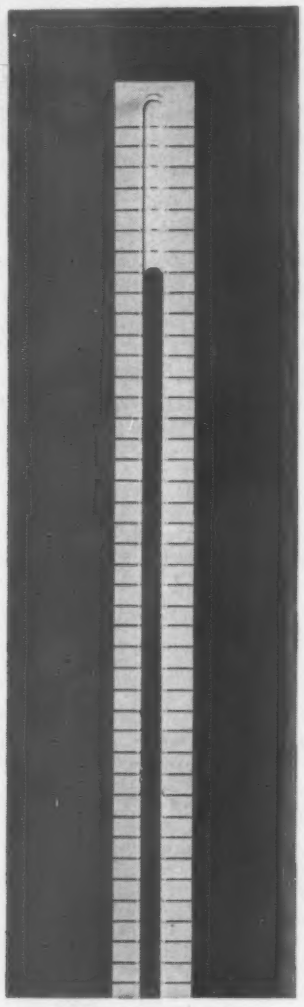
Naturetin, the diuretic of choice, also possesses marked antihypertensive properties, thus complementing the known antihypertensive action of Raudixin. In this way a lower dose of each component in Rautrax-N controls hypertension effectively with few side effects and greater margin of safety.[1-16]

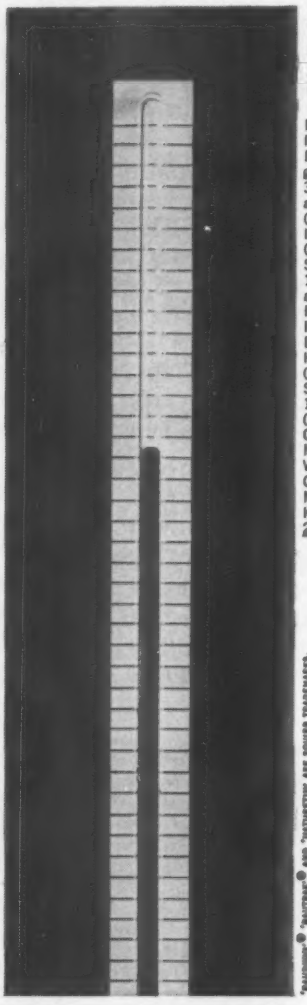
Other advantages are a balanced electrolyte pattern[1-16] and the maintenance of a favorable urinary sodium-potassium excretion ratio.[2-16] Clinical studies[1-5] have shown that the diuretic component of Rautrax-N—Naturetin—has only a slight effect on serum potassium. The supplemental potassium chloride provides additional protection against potassium depletion which may occur during long term therapy.

Rautrax-N may be used alone or in conjunction with other antihypertensive drugs, such as ganglionic blocking agents, veratrum or hydralazine, when such regimens are needed in the occasionally difficult patient.

Supply: Rautrax-N—capsule-shaped tablets providing 50 mg. Raudixin (Squibb Rauwolfia Serpentina Whole Root) and 4 mg. Naturetin (Squibb Benzydroflumethiazide), with 400 mg. potassium chloride.

Dosage: Initially-1 to 4 tablets daily after meals. Maintenance-1 or 2 tablets daily after meals; maintenance dosage may range from 1 to 4 tablets daily. For complete instructions and precautions see package insert. Literature available on request.





References: 1. Reports to the Squibb Institute, 1960. 2. David, N. A.; Porter, G. A., and Gray, R. H.: Monographs on Therapy 5:60 (Feb.) 1960. 3. Stenberg, E. S., Jr.; Benedetti, A., and Forsham, P. H.: Op. cit. 5:46 (Feb.) 1960. 4. Fuchs, M.; Moyer, J. H., and Newman, B. E.: Op. cit. 5:55 (Feb.) 1960. 5. Marriott, H. J. L., and Schamroth, L.: Op. cit. 5:14 (Feb.) 1960. 6. Ira, G. H., Jr.; Shaw, D. M., and Bogdonoff, M. D.: North Carolina M. J. 21:19 (Jan.) 1960. 7. Cohen, B. M.: M. Times, to be published. 8. Breneman, G. M. and Keyes, J. W.: Henry Ford Hosp. M. Bull. 7:281 (Dec.) 1959. 9. Forsham, P. H.: Squibb Clin. Res. Notes 2:5 (Dec.) 1959. 10. Larson, E.: Op. cit. 2:10 (Dec.) 1959. 11. Kirkendall, W. M.: Op. cit. 2:11 (Dec.) 1959. 12. Yu, P. N.: Op. cit. 2:12 (Dec.) 1959. 13. Weiss, S.; Weiss, J., and Weiss, B.: Op. cit. 2:13 (Dec.) 1959. 14. Moser, M.: Op. cit. 2:13 (Dec.) 1959. 15. Kahn, A., and Grenblatt, I. J.: Op. cit. 2:15 (Dec.) 1959. 16. Grollman, A.: Monographs on Therapy 5:1 (Feb.) 1960.

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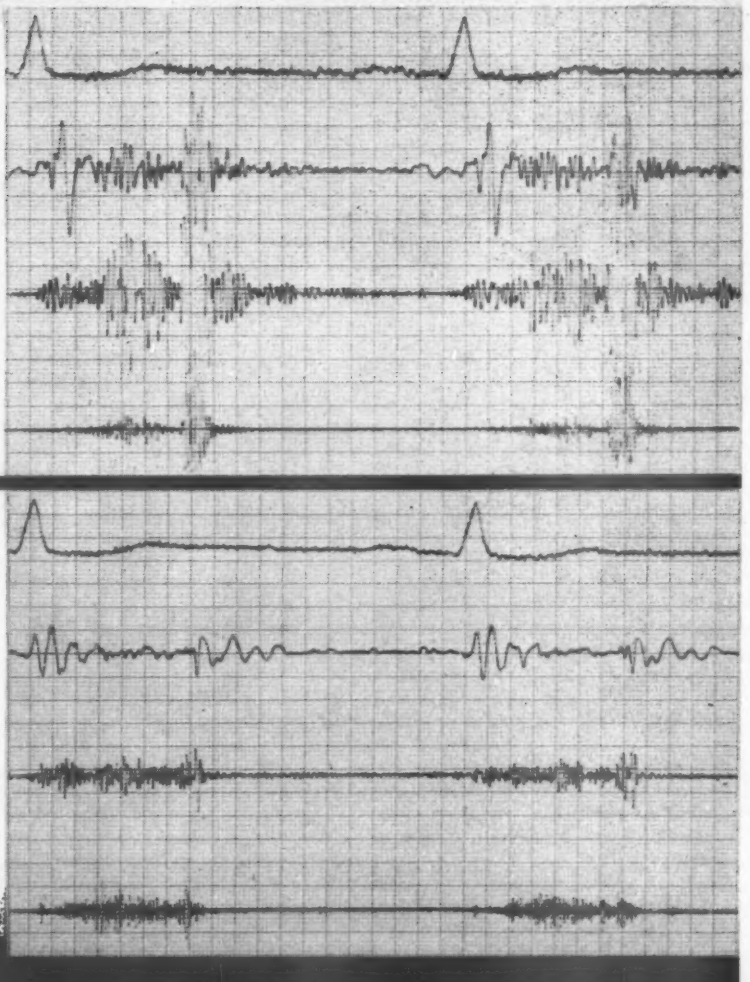
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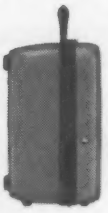
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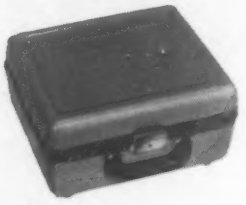
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***Fuchs, M.: A review of the thiazide pharmacology, Paper presented at Puerto Rican M. Soc., San Juan, Puerto Rico, Jan., 1960.**

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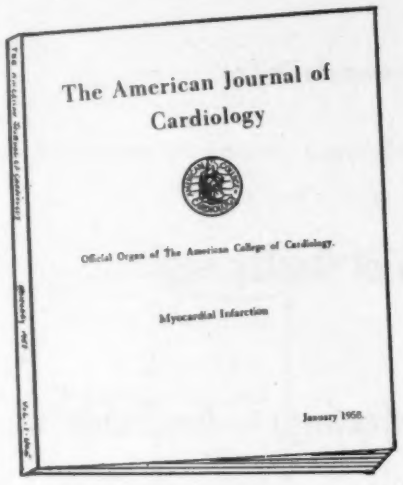
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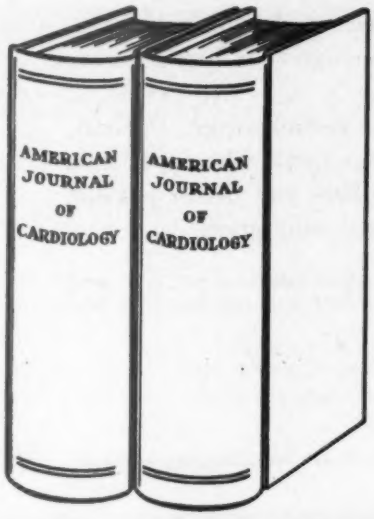
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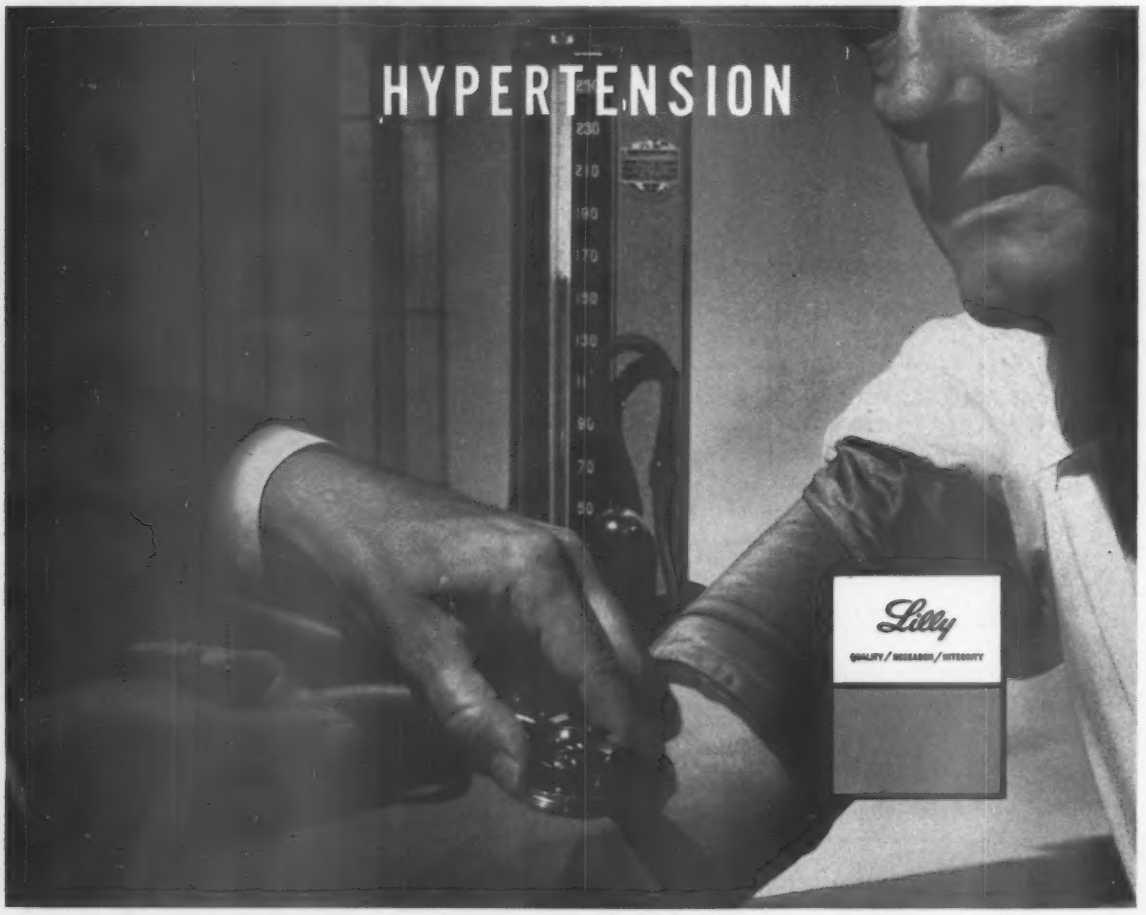
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1. Geriatrics, *12*:185, 1957.
2. J. Indiana M. A., *48*:603, 1955.

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The American Journal of Cardiology

VOLUME VI SEPTEMBER 1960 NUMBER 3

Symposium on Persistent Atrioventricular Canal

Introduction

EMBRYOLOGY

IN the primitive heart, a canal separates the auricle from the ventricle. Normally, this canal divides longitudinally (vertically) following the appearance of two cushions, one anterior and one posterior, which progress toward each other, meet and fuse together. The septum thus formed (intermediate septum) meets the interauricular septum above and joins the upper membranous portion of the interventricular septum below, dividing the primitive heart into right and left hearts.

Simultaneously, another process occurs. On the right and left, cushions appear at the extremity of the anterior and posterior cushions, respectively. When the two primitive elements of the intermediate septum unite, these cushions fuse and project longitudinally to form, on the right, the septal cusp of the tricuspid valve and, on the left, the larger cusp of the mitral valve. These two auriculoventricular valves are, therefore, formed by the union of two primitive semivalves. Other cushions appear at the same level, on the lateral border of the auriculoventricular canal (one on the left, two on the right) and develop similarly to form the smaller mitral valve cusp on the left and the anterior and posterior cusps of the tricuspid valve on the right. This seems to be the embryological evolution of the two auriculoventricular orifices and their valvular system.

The abnormal formation of the intermediate septum is the essential anomaly in the development of this region. If the two vertical cushions do not meet, a hiatus results. The two lateral cushions they bear will not fuse. A further consequence is the lack of fusion of the two semivalves, which normally would form the larger mitral valve cusp and the septal cusp of the tricuspid valve. A slit separating these two valves into two more or less deep and equal portions will occur. This process constantly affects the left side, whereas the right side may remain untouched. The two essential types of this malformation include: (1) the partial form, wherein the mitral valve alone is cleft and (2) the total form, wherein the tricuspid valve is also cleft. Both the mitral and tricuspid valves meet either in front or at the back. Each one forms a sort of common valvular band which projects from the right to the left ventricle, passing like a bridge above the interventricular septum. A sagittal hiatus will then divide throughout their length these two common auriculoventricular formations.

This defect in the development of the intermediate septum occurs not only horizontally, but may occur also vertically. In the latter case, the intermediate septum can no longer meet the interauricular septum above; a defect will result at this site in the shape of a low atrial septal defect of the ostium primum type which, therefore, seems to spring not from a flaw in the development of the interauricular septum, but primarily from a faulty development of

the intermediate septum. A similar defect appearing below will determine a ventricular septal defect.

It seems that the faulty development of the intermediate septum is the cause of the abnormalities of the auriculoventricular orifices and their valvular system, on the one hand, and of the atrial septal defects of the ostium primum type, on the other. Therefore, persistent A-V canals are related to atrial septal defects of which they are but a special form.

Classification of Defects

A gamut of malformations deriving from the same embryological process may be encountered:

(1) An ostium primum defect, with the mitral valve alone being cleft, represents the partial form of atrioventricular canal.

(2) An ostium primum defect with cleft mitral and tricuspid valves, represents the complete form of atrioventricular canal.

(3) A large variety of anatomical formations may connect together the two auriculoventricular bands of the complete form. These formations, in addition, are often attached to the upper border of the interventricular septum by aberrant cords or an irregularly perforated network of fibrous tissue. Although they originally had been grouped under the denomination of "intermediate forms," the present tendency of certain authors is to eliminate this additional division and to classify these malformations with the complete forms.

(4) Similarly, all forms of interventricular communications lying below the valvular system would fall into the complete form of atrioventricular canal.

(5) I shall not dwell upon the association of the numerous secondary anomalies affecting the development of a cleft valve, of the cords (their number, insertion, etc.) or on the unusually fleshy aspect of defective valves.

(6) Also to be noted is the frequent association of other defects, such as a second atrial septal defect of the ostium secundum type, a moderate pulmonary stenosis and patent ductus arteriosus.

(7) Worthy of emphasis is that an isolated ostium primum defect seems to result from the process just described and is actually a minor malformation of this group.

(8) A single auricle, being the cause of a trilocular, biventricular heart, may take the shape of an ostium primum defect or of an extensive ostium secundum defect. According to the case, this defect will fall into the category of atrial septal defects or of persistent atrioventricular canals.

(9) Likewise, isolated mitral clefts may exist which, despite a different semeiological picture, most certainly spring from the same pathological source. The association of a cleft mitral valve with an atrial septal defect of the ostium secundum type is infrequent but should be considered as a transitional stage between these various affections. And finally, in rare cases, large atrial septal defects of the ostium secundum type may be found to have the clinical characteristics of the ostium primum type.

Clinical Aspects

Because we wish these facts and notions to be precisely stated, we requested the highly qualified opinions of the participants in this symposium. Their eloquent accounts show that the group of persistent atrioventricular canals presents a remarkable unity justifying their nosological classification, but at the same time a certain amount of diversity due to the isolated anomalies which represent so many minor or transitional forms.

Based on his experience with 300 cases, Bedford applies these embryological findings clinically and places the atrioventricular canal properly in the large group of atrial septal defects.

The key to the differential diagnosis lies in the remarkable electrical property of the ostium primum defect in which is presented a left axis deviation with clockwise rotation of the frontal vectorcardiogram. This fact calls for comment, for the left axis deviation first detected in persistent atrioventricular canals had first been attributed, in such cases, to the effect on the left ventricular muscle of the mitral insufficiency resulting from the mitral cleft. This does not seem to be a correct interpretation of the phenomenon; Burchell, DuShane and Brandenburg bring us a particularly critical and documented study from which it may be concluded that this remarkable electrical peculiarity seems to be the consequence of low-seated septal defects, since the malformation affects a portion of the left bundle branch.

The surgical treatment of persistent atrioventricular canals consists in the repair of the auriculoventricular valves by sutures when they are cleft, the approach to the mitral valve being via the right auricle through the ostium

primum. The septal defect is then closed either with direct suture or, more generally, with a prosthetic patch. This intervention, elegant in its conception, takes time; the consensus is that the use of extracorporeal circulation is indispensable. The most critical time is that of the placing of the first sutures on the upper border of the interventricular septum, i.e., in the region of the bundle of His.

Successively, Ellis, McGoon and Kirklin, Cooley and then Dubost and Blondeau describe the difficulties encountered during surgery and the results obtained. Later, Crafoord and Senning present their personal technic of repair of the interventricular septum and of the hiatus which, in the complete forms, separates the two (anterior and posterior) valvular bands.

The operative results differ widely with the gravity of the defect. In partial forms, the percentage of failure is approximately 5 per cent. In grave forms, however, the mortality reaches 66 per cent.

We should like to convey our thanks to the eminent authors who so willingly accepted the invitation to take part in this symposium. To them we owe another important advance in our knowledge of this particularly delicate subject.

R. Heim de Balsac, M.D.
Paris, France



The Anatomical Types of Atrial Septal Defect

Their Incidence and Clinical Diagnosis

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London, England

Since Rokitansky's[1] time, it has been customary to divide atrial septal defects into ostium primum and ostium secundum types, but this simple grouping is inadequate for surgical purposes. Older pathological descriptions often portrayed an atrial septal defect (ASD) from the left side. The surgeon, however, must relate it to the main anatomical landmarks in the right atrium; namely, the two caval orifices, the Eustachian valve, the coronary sinus, the fossa ovalis and the tricuspid valve (Fig. 1A).

Anatomical Classification

The following anatomical classification is based on observations made at open heart surgery on 180 patients with ASD operated on at the Middlesex Hospital by Mr. Holmes Sellors and his colleagues, on the examination of many specimens assembled by Dr. R. Hudson at the Institute of Cardiology and on published pathological accounts.[1–4]

Fossa Ovalis Defects (*Ostium Secundum Defect*): (1) *Central* and completely surrounded by a border of atrial septum. If some part of the valve of the fossa ovalis is present, the defect may be confined to the upper part of the fossa or may be fenestrated (Fig. 1B). (2) *Inferior caval type* lying astride the caval orifice, which thus opens into both atria, as described by Rokitansky. There is no lower margin to the defect and, sometimes, the posterior margin is lacking, so that the right pulmonary veins open into both atria. The Eustachian valve, if present, is continuous with the anterior limb of the annulus ovalis so that the margin of the septal defect takes a spiral course. A profuse Chiari network sometimes obscures the lower pole of the defect (Figs. 1C, 1D and Fig. 4).

Superior Caval Defects (*Sinus Venosus Defect*): The defect underlies the superior caval orifice, which thus opens into both atria; there is no upper margin and often the posterior margin is incomplete. The right pulmonary veins are anomalous. Usually, the upper vein opens into the superior vena cava, a middle vein (or veins) opens into the right (or both) atria level with the defect and a lower vein opens, normally, into the left atrium (Fig. 1E).

Atrioventricular Defects (*Ostium Primum Defect; Endocardial Cushion Defect; Partial or Complete Common Atrioventricular Canal*): The ostium primum type of ASD overlies the ventricular septum and attached mitral and tricuspid valve leaflets, its upper border being crescentic (Fig. 1F). The anterior cusp of the mitral valve is usually cleft or malformed and sometimes the septal cusp of the tricuspid is similarly affected. When the cleft in these mitral and tricuspid leaflets is continuous across the ventricular septum, there is a common atrioventricular canal with anterior and posterior valve leaflets. Usually, the upper part of the ventricular septum, below the common atrioventricular (A-V) valves, is defective and permits a ventricular shunt; but, occasionally, the subvalvular space is more or less filled by aberrant papillary muscles and chordae, so that there is little or no ventricular defect. Patients with this type of defect may survive to adult life. Occasionally, rheumatic mitral stenosis is superimposed on the malformed valve of a primum defect.[5–7]

Ostium primum defects may thus be classified anatomically as follows (See Fig. 2): (1) with normal A-V valves; (2) with cleft or malformed anterior mitral cusp; (3) with cleft mitral and cleft or malformed septal cusp of tricuspid; (4) with common atrioventricular canal: (a) with significant ventricular septal defect; (b) with insignificant ventricular septal defect.

Incidence

The incidence of these various anatomical types in 170 consecutive surgical cases (exclud-

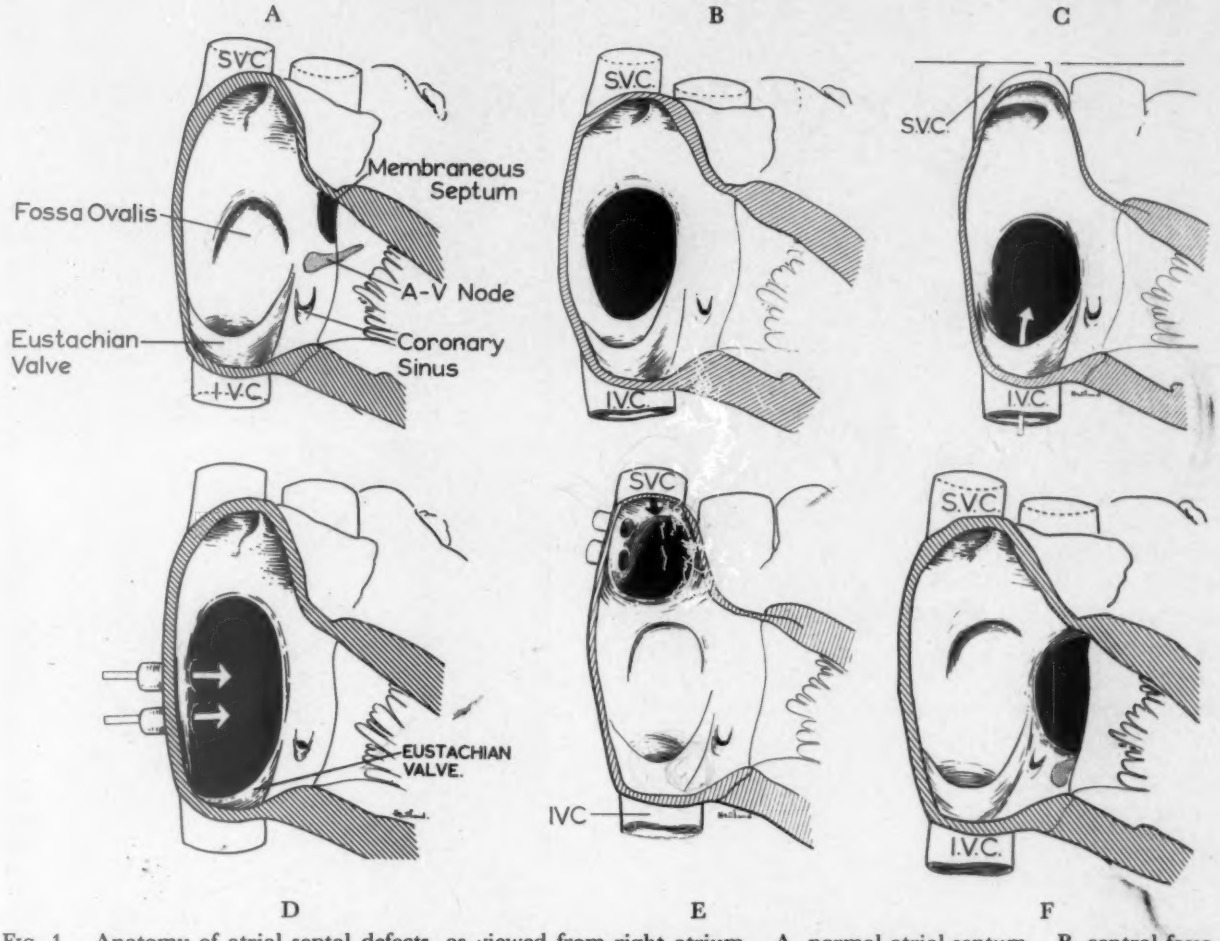


FIG. 1. Anatomy of atrial septal defects, as viewed from right atrium. A, normal atrial septum. B, central fossa ovalis defect. C, inferior caval defect with large Eustachian valve; vena cava opens into both atria. D, large inferior caval defect with no posterior margin; pseudo-anomalous right pulmonary veins. E, superior caval (sinus venosus) defect; anomalous right upper and middle pulmonary veins. F, atrioventricular (ostium primum) defect. (From: BEDFORD, D. E., SELLORS, T. H., SOMERVILLE, W., BELCHER, J. R. and BESTERMAN, E. M. M. Atrial septal defect and its surgical treatment. *Lancet*, 1: 1255, 1957.)

ing the ostium primum defects) was as follows:

Central fossa ovalis type	115 (67.6%)
Inferior caval type	44 (26%)
Superior caval type	9 (5.3%)
Almost total defect	1
Double defect with cor triatriatum	1

Ostium Primum Defect: The incidence of ostium primum defects is far greater in infants and young children than it is in adults because few patients with common A-V canal survive longer than four years. Thus, Keith et al.[8] give the incidence of primum defects in a children's hospital as just over 25 per cent of all cases of ASD; whereas, in 300 cases of ASD investigated at the Middlesex Hospital, in which all patients were over five years of age and 60 per cent were over twenty, the diagnosis of primum defect was made in thirty-one cases (10.3 per cent).

We excluded these patients from surgery under hypothermia; but fifteen of them have now been operated on and the diagnosis was confirmed in fourteen, the exception being a patient with a ventricular septal defect with left ventricular-right atrial shunt through a malformed tricuspid valve. From this experience, we estimate that the incidence of ostium primum defect in all patients over five years of age with ASD does not exceed 10 per cent.

The anatomical types of primum defect in fifteen proved cases, in which the subjects were seven to forty-four years of age, was as follows:

Normal A-V valves	2
Cleft mitral valve	7
Cleft mitral and tricuspid valves	3
Common A-V canal	3

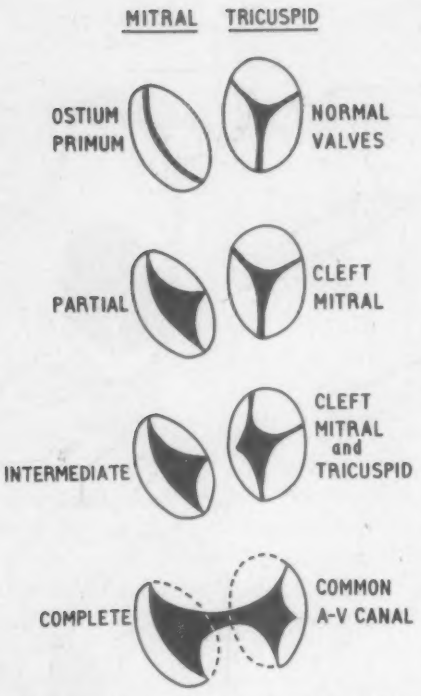


FIG. 2. Diagram of mitral and tricuspid orifices viewed from above (atrial aspect) showing valve lesions associated with ostium primum defects. Partial, intermediate and complete forms of common A-V canal (Mayo Clinic terminology) indicated on left.

ASSOCIATED LESIONS

The following complications, excluding primum defects, were found at operation in a series of 170 cases:

Mitral stenosis	14 (8%)
Mitral incompetence	3
Persistent left superior vena cava	9
Mild pulmonary valve stenosis	8
Anomalous right upper pulmonary veins	10
Right-sided aortic arch	1
Pseudo-anomalous right pulmonary veins (fossa ovalis defect with no posterior rim)	10

These statistics pertain to surgical patients in whom ASD was judged to be the sole or main lesion. Of course, an ASD is common in many complex congenital malformations as well. Right-sided aortic arch is so rare in uncomplicated secundum defects that its presence is an indication that the diagnosis must be carefully scrutinized. Ostium primum defects in infants are often complicated by other lesions.

In two of our subjects (ages six and thirty-three years), diagnosed clinically, the inferior vena cava was absent (persistent right posterior



FIG. 3. A six year old boy with ostium primum defect. Anterior and lateral views. Angiocardiogram via saphenous route showing venous return from lower part of body to superior vena cava via a dilated azygos vein (persistent right posterior cardinal vein).

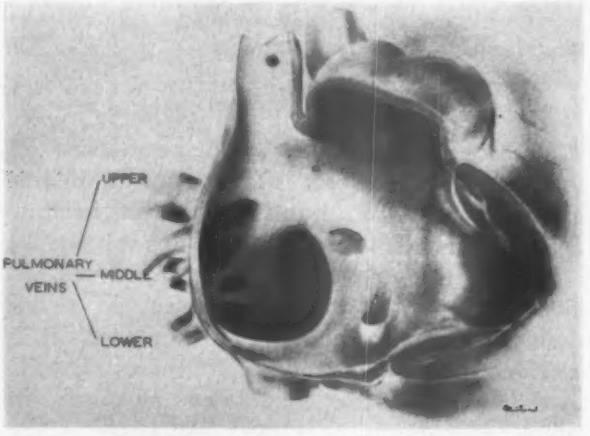


FIG. 4. Pathological specimen from man aged thirty-nine, showing inferior caval defect with no posterior margin and right pulmonary veins entering common atrial wall. Inferior vena cava opens into both atria.



FIG. 5. Overpenetrated roentgenogram showing opacities within right atrial border due to entry of enlarged right pulmonary veins. At operation, there was a large defect with no lower or posterior margins.



FIG. 6. Postoperative angiocardiogram (lateral view) via saphenous route, showing inferior vena cava opening almost entirely into left atrium and shut off from right atrium by the Eustachian valve, which has been incorporated in the suture line, and which is seen ballooned into right atrium. This was successfully corrected by re-operation.

cardinal vein). This combination, which has been described by others,[9,10] deserves mention because of its surgical implications. Venous blood from the lower part of the body is returned to the superior vena cava via a dilated azygos vein (Fig. 3) which, in one case, was noted in the plain roentgenogram.

Clinical Diagnosis

For surgical purposes, it is important to make the clinical diagnosis as complete as possible. Primum defects require extracorporeal circulation for their surgical repair. Other types, however, can safely be repaired under hypothermia, provided that the surgeon identifies the anatomy and complications prior to arresting the circulation. This can be done quickly if the surgeon knows what to look for.

Fossa Ovalis Defects: The diagnosis of uncomplicated fossa ovalis defects needs little discussion. It depends essentially on finding a left-to-right shunt at atrial level, usually confirmed by passage of the catheter through the defect. The important clinical signs are a pulmonary systolic ejection murmur, a persistently split second sound,[11] a short delayed tricuspid diastolic murmur, an electrocardiogram showing right axis deviation combined with incomplete right bundle branch block and a characteristic roentgenogram.

Fossa ovalis defects, in which the right pulmonary veins appear to be anomalous at catheterization, usually prove to have no posterior margin, so that the veins actually communicate with both atria (Fig. 4). Sometimes, large anomalous pulmonary veins are evident in overpenetrated films, or in tomograms, as rounded opacities within the right atrial border. This was first pointed out to me by Dr. Peter Kerley in the film reproduced in Figure 5.

Inferior Caval Defects: These can be demonstrated by angiography if the contrast medium is injected into the inferior vena cava, just below its entry into the right atrium, by means of a catheter passed via the saphenous route. In closing this type of defect, it is easy to in-



FIG. 7. Superior caval defect. Selective angiocardiogram by saphenous route showing right upper pulmonary vein entering dilated proximal extremity of superior vena cava, and middle vein entering adjacent right atrium.

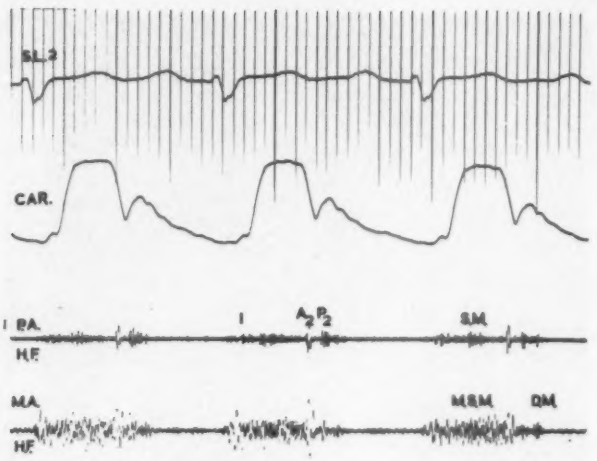


FIG. 8. Phonocardiogram from girl aged nineteen with ostium primum defect and cleft mitral valve, showing split second sound at pulmonary area and pansystolic and diastolic murmurs at mitral area.

corporate the Eustachian valve in the suture line, in which case the caval opening may be stenosed or deflected into the left atrium. This mishap can be demonstrated by postoperative angiography (Fig. 6).

Superior Caval Defects: These can almost always be diagnosed. There is a localized distention of the superior vena cava just above the right atrium, at the site of entry of the anomalous right upper pulmonary vein, which is usually evident in roentgenograms, if sought. The enlarged right pulmonary arterial branches tend to obscure this segment of the superior vena cava, but an overpenetrated film or a tomogram will show it. Angiocardiograms will also show the anomalous right pulmonary veins (Fig. 7).

The right upper and middle pulmonary veins can usually be entered at catheterization, and gas analysis shows a higher oxygen saturation in the lower part of the vena cava than in venous blood withdrawn higher up. In this type of ASD, it is important to detect a persistent left superior vena cava, if present. This is a great surgical asset, since it permits ligation of the right superior vena cava above the entry of the right upper pulmonary vein, after which the right caval opening can be deflected into the left atrium in suturing the defect.

Anomalous right pulmonary veins, of the same pattern as those found in superior caval defects, were encountered at surgery in two other subjects, one with a fossa ovalis defect and the other with mitral stenosis and an aneurysm of the fossa ovalis without any overt septal defect.

Atrioventricular (Ostium Primum) Defects: These defects can almost always be diagnosed by means of clinical signs and electrocardiograms, sometimes aided by catheter findings.

Patients encountered in the pediatric clinic may have large hearts, pulmonary hypertension, physical and mental retardation or mongolism. They are often subject to infection of the respiratory tract and heart failure usually develops in the first few years of life. In older patients, however, the clinical picture may be far more benign. In my fifteen proved cases, in which the patients were seven to forty-four years of age (average sixteen years), only five were slightly undersized and two were mentally retarded, but none was mongolian.

The oldest patient, aged forty-four, served in the Navy for nine years until he became cyanotic, after which he worked as a driver up to the time of his final illness. Necropsy showed a primum defect, a common A-V canal without significant ventricular septal defect and organized thrombosis of both main pulmonary arteries.

Survival until sixty to seventy years has been recorded; for example, one of Rokitansky's subjects was aged sixty-one and, in two recorded cases, patients having primum defect with mitral stenosis were aged sixty and seventy-two years.[6,7] In contrast to secundum defects, the sex incidence in the primum type is about equal. In my series, there were eight males to seven females.

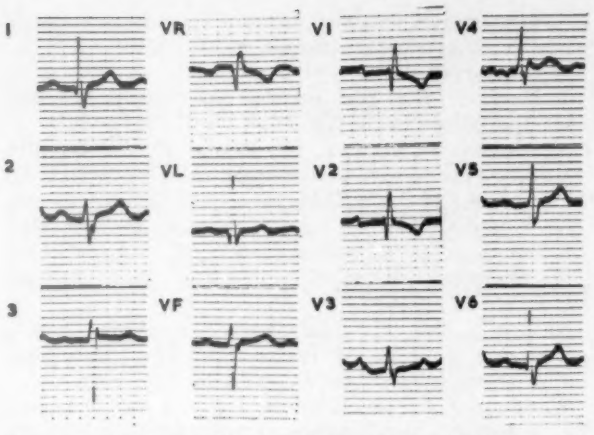


FIG. 9. Electrocardiogram from girl aged sixteen with ostium primum defect and cleft mitral valve, showing left axis deviation and rSR pattern in lead V_1. P-R interval 0.22 second.

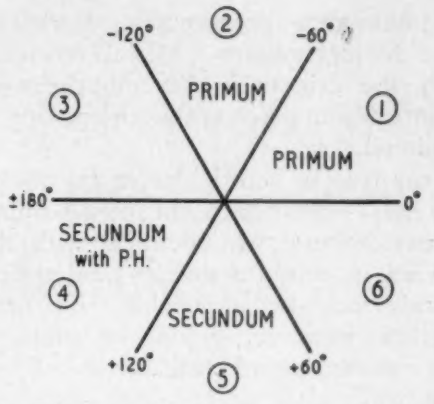


FIG. 10. Diagram of triaxial system showing usual distribution of electrical axis of QRS in sextants 1 and 2 in ostium primum defects, and in sextants 4 and 5 in ostium secundum defects; those with obstructive pulmonary hypertension (P.H.) tend to fall into sextant 4.

A grossly enlarged heart is common, but not invariable. In my subjects, the cardiothoracic ratio was 50 to 55 per cent in five, 55 to 60 per cent in three and over 60 per cent in seven. Slight left atrial enlargement was detected on roentgenograms in eight instances.

On physical examination, the apex beat may suggest a left ventricular thrust in contrast to the tap or diffuse right ventricular lift that is usual in secundum defects. The most important clinical sign is a pansystolic murmur, often accompanied by a systolic thrill at the apex and over the right ventricle, due to mitral or tricuspid incompetence or both (Fig. 8). A short delayed diastolic murmur over the right ventricle is the rule in secundum defects. In primum defects, however, this murmur is often longer, louder and better heard at the apex. In one case, there was a diastolic thrill. These murmurs may closely simulate those of rheumatic mitral disease, so that the term "false Lutembacher syndrome"[12] has been coined.

The electrocardiogram provides the best evidence of a primum defect. In fourteen of my fifteen subjects, it showed left axis deviation in the standard leads combined with incomplete right bundle branch block pattern in the chest leads (Fig. 9). The frontal vectorcardiogram was also characteristic.[13] The only exception was the forty-four year old patient with pulmonary hypertension and reversed shunt, whose electrocardiogram showed right axis deviation. Campbell and Missen[14] reported a somewhat similar case.

It is useful to plot the electrical axis of QRS in the triaxial system,[15] as shown in Figure 10. This electrocardiographic pattern, typical of primum defects, also occurs in other conditions. For example, it sometimes occurs in ventricular septal defects; but this does not diminish its value in distinguishing between a primum and a secundum defect when an atrial shunt has been demonstrated. Some degree of A-V block is more frequent than in secundum defects and, in seven of my fifteen subjects, the P-R interval exceeded 0.20 second.

Cardiac catheterization may suggest a shunt at both atrial and ventricular levels even when there is no ventricular septal defect. The left ventricle is more readily entered than usual and the catheter may pass directly from right atrium to left ventricle and vice versa. The level at which the catheter traverses the ASD is not a reliable guide, since inferior caval defects are located lower than primum defects.

In my subjects, the pulmonary artery pressure was normal in four, 30 to 50 mm. Hg systolic in eight and 80 mm. Hg systolic in one, aged nine, with a common A-V canal. The remaining subject, aged forty-four, not catheterized, had hypertension due to pulmonary thrombosis. It appears that pulmonary hypertension exceeding 50 mm. Hg systolic occurs in children only if there is a common A-V canal with a significant ventricular shunt.

DIFFERENTIAL DIAGNOSIS

A primum defect has to be distinguished from a secundum defect with rheumatic mitral disease. Lutembacher's disease is rarely encountered below the age of twenty-five, and the electrocardiogram always shows right axis deviation. Other points to be borne in mind at diagnosis are a rheumatic history, atrial

fibrillation and, occasionally, Kerley's lines in the roentgenogram. Mitral murmurs are usually less evident in Lutembacher's disease then in primum defects, and an opening snap is exceptional.

In my case of ventricular septal defect with direct left ventricular-right atrial shunt, the electrocardiogram was identical with the one described in primum defects, and differential diagnosis may be impossible. Neither malformation, however, should be submitted to surgery under hypothermia.

Summary

The anatomical varieties of atrial septal defect are described and their clinical diagnosis is discussed on the basis of experience in investigating a series of 300 subjects and of observations made at operation on 180 of them. In particular, the diagnosis of atrioventricular (ostium primum) defects is discussed. It can be made almost always on the basis of typical clinical signs and electrocardiogram, sometimes aided by cardiac catheterization.

Acknowledgment

Investigation of a large series of subjects before, during and after surgery represents the work of a team, and I wish to thank my colleagues, Drs. W. Somerville, E. Besterman, T. O'Donnell, J. Somerville and M. J. Goldberg, who have shared in the work on which this paper is based. I also wish to express my thanks to Mr. T. Holmes Sellors and his surgical colleagues for their constant cooperation, to Dr. Reginald Hudson who has examined all my specimens, and to Drs. Peter Kerley and J. N. Pattinson who have been responsible for our roentgenograms and who have helped and advised us in many ways.

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The Electrocardiogram of Patients with Atrioventricular Cushion Defects (Defects of the Atrioventricular Canal)*

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KNOWLEDGE OF THE anatomic varieties of atrial septal defects seen in the Mayo Clinic has stemmed mainly from the studies of Rogers and Edwards[1] reported in 1948. The value of the electrocardiogram in discriminating between the usual type of atrial septal defect and the low atrial defect in the region of the atrioventricular valves was recognized much later, but was established at the time intracardiac operations with the aid of the heart-lung machine were routinely being performed during 1955. Isolated case reports had drawn attention to the unusual left axis deviation associated with low atrial defects, and Milnor and Bertrand[2] mention that in 1953 Taussig had, for some time, been utilizing the electrocardiogram for differentiating among types of atrial septal defects. Blount mentioned the diagnostic value of the electrocardiogram in 1954, and he and his associates presented a paper[3] on the subject in 1956.

Later in 1956, the experience of the Mayo Clinic in specifically relating electrocardiographic aberrations to defects of the lower atrial septum and deformities of the atrioventricular canals was published by Toscano-Barboza and two of us.[4] In this communication, some vectorcardiographic analyses were made, with descriptions of different types of frontal QRS loops. It was claimed that the evidence favored a congenital aberration of ventricular excitation and that the electrocardiographic phenomena were not primarily caused by left ventricular hypertrophy consequent to mitral incompetence.

The conclusion that mitral incompetence was not the direct cause of the marked left axis deviation arose from the following observations: (1) newborn children with defects of the atrioventricular canal already had the diagnostic tracings, (2) the association of pulmonary stenosis did not obscure the unusual excitatory pattern and (3) the electrocardiographic records did not correlate with the size of the left ventricle as depicted in the roentgenogram or as seen at operation or necropsy; nor did they correlate with the assessment of the degree of mitral regurgitation by the surgeon. Indeed, the typical electrocardiogram was found in cases in which the mitral valve was judged to be competent by the surgeon or the anatomist. An additional conclusion was deduced from the fact that, in acquired rheumatic mitral regurgitation associated with an atrial septal defect, the patients' electrocardiograms did not show the initial QRS vectors rotating counterclockwise in the 0° to −90° quadrant. This was believed to lend powerful support to the contention that mitral insufficiency *per se* was not the important factor in producing the left axis deviation in patients with septal defects of the atrioventricular canal type (atrioventricular cushion defects).

Toscano-Barboza and his co-workers[4] pointed out that the electrocardiograms characteristically associated with defects of the atrioventricular canal might be identical to those associated with coronary disease and acquired aberrations in ventricular excitation. It is of interest that Milnor and Bertrand,[2] favoring the view that the left axis deviation was to be related to mitral insufficiency, reproduced typical scalar electrocardiograms and vectorcardiograms of a patient proved later to have a low

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atrial septal defect but competent tricuspid and mitral valves. However, as there was severe narrowing of the anterior branch of the left coronary artery, they chose, between the two causal possibilities, to ascribe the electrocardiographic abnormality to the coronary disease. They concluded, on the basis of their experience (limited at that time), that persistent ostium primum with no functional abnormality of the mitral valve could not be distinguished electrocardiographically from persistent ostium secundum. The electrocardiogram in Case 4 of their communication,[2] showing right axis deviation with apparent clockwise rotation of the sequential instantaneous vectors, is indisputable evidence for this conclusion. They mention that the mitral valve may be competent even though a cleft is present in the aortic leaflet: a viewpoint that is in accord with ours.

That mitral incompetence may contribute to left axis deviation cannot be denied. However, the evidence seems to point convincingly to the fact that it is not essential to left axis deviation. Nevertheless, the opposite opinion is still favored in a number of centers, as witnessed by the reports of Cooley and McNamara,[5] and Campbell and Missen.[6]

Liang and Schwantje[7] discussed the electrocardiograms of five patients with primum defects and interpreted the records in three to indicate left ventricular hypertrophy, which correlated well with the finding of significant mitral insufficiency at operation. However, in the absence of mitral insufficiency, there was no left ventricular hypertrophy, although the axis remained deviated to the left. They reported left axis deviation and a prolonged P-R interval in all their patients with primum defect.

Ostium Primum Defects Without Characteristic Electrocardiogram: Our experience has led us to the belief that, in a young person with congenital heart disease and a known large left-to-right transatrial shunt, the presence of the typical frontal vectorcardiogram with vectors rotating counterclockwise above the isoelectric line may be practically pathognomonic of defects in the region of the atrioventricular valves. This statement, however, may be reversed and put in the form of the following question: "What percentage of patients with defects of the ostium primum type do not have a characteristic electrocardiogram?"

We have not seen any patients who had proved defects of the complete form of a common atrioventricular canal who also had electrocardiograms that were not consistent with the pattern described herein as being characteristic of patients with such defects. In patients with either the incomplete form or the atypical lesions more questionably related to deformities of the atrioventricular canal, the following electrocardiographic exceptions to the characteristic template have been encountered:

1. Postmortem examination of a twenty-seven year old woman showed a low atrial septal defect of the ostium primum type with fusion of cleft bicuspid and mitral leaflets over the top of the septum. The electrocardiograms showed a normal axis deviation and a clockwise-rotating frontal loop. This patient was seen on one occasion only, in 1951; she was cyanotic (arterial oxygen saturation 84 per cent), had severe pulmonary hypertension and her right ventricular pressure (145/4) exceeded that in the left ventricle (100/2).

2. The electrocardiogram of a ten year old child was thought by all three of us not to favor an atrioventricular cushion defect because of persistent vectors, as projected in the frontal plane, in the $+45°$ to $+60°$ zone, the clinical diagnosis being an atrial septal defect and mitral insufficiency. At operation, a typical incomplete form of atrioventricular canal defect with moderate mitral insufficiency was found.

3. The electrocardiogram of a seven year old child showed multiphasic QRS complexes in leads III and aVF, in which the areas under the QRS deflection were greater above than below the isoelectric line, in which the designation of right axis deviation would be proper and in which an accurate construction of the vectorial loops from the scalar leads would be impossible. The vectorcardiographic loop showed a horizontally disposed narrow "figure-of-eight" loop, almost all of which was below the isoelectric point. The preoperative diagnosis was either an ostium secundum or an ostium primum defect. At operation, the latter, *i.e.*, a typical atrioventricular cushion defect or partial form of atrioventricular canal, was found and corrected.

4. The electrocardiogram of a ten year old child showed normal axis deviation. At operation, the child was found to have a moderate-sized, usual-type atrial septal defect (ostium secundum type) but a cleft mitral leaflet with moderate mitral insufficiency.

5. The electrocardiogram of a two year old child did not suggest an atrioventricular cushion defect either. At operation, however, two ventricular septal defects were found, one of which was posterior and associated with tricuspid deformity. The situation was appraised by the surgeon as being similar to defects of the atrioventricular cushion type, *although the atrial septum was intact.*

6. In a six month old cyanotic infant who had a greatly enlarged heart and *right axis* deviation in the

electrocardiogram, the diagnosis of atrioventricular canal was tentatively made from cardiac catheterization data and later proved at postmortem examination.

Attention may also be drawn to a patient described in the case records of the Massachusetts General Hospital[8] who was later shown to have a complete atrioventricular canal deformity associated with pulmonary stenosis and whose electrocardiogram did not show left axis deviation. Through the kindness of Dr. Friedlich, one of us (H. B. B.) has had the opportunity to review these records and agrees that they would not suggest the diagnosis in this instance.

Mouquin and his co-workers[9] have published an account of three cases of tetralogy with common atrioventricular canal, illustrated with complete electrocardiographic leads. We would interpret these as typical or suggestive of the diagnosis, there being evidence of the counterclockwise rotation of the instantaneous QRS vectors, with the late vectors to be associated with the right ventricular hypertrophy.

Ziegler[10] has published an electrocardiogram of a five year old child that does not show diagnostic features, which supports his statement that the electrocardiogram *per se* does not necessarily exclude a primum type of defect. Forrest[11] has reported that one of three patients with ostium primum defects did not show left axis deviation. This case, however, may be open to question regarding the correctness of the diagnosis, since it was reported that the postmortem examination revealed a right atrial-left ventricular communication without involvement of the mitral valve.

It is difficult to understand the observations of Witham and Ellison,[12] which contrast so sharply with ours. These authors reported on five patients, none of whom had a typical electrocardiogram. In four of the five records reproduced, there was right axis deviation. In these cases, however, there was no proof of the actual lesion existing. Therefore, in the ultimate scoring of electrocardiographic accuracy in diagnosing the condition under discussion, the use of these cases might be challenged.

Other Electrocardiographic Studies: In a recent discussion of persistent ostium primum in the symposium on congenital heart disease at the British Cardiological Society,[13] there was division of opinion as to the specificity of the electrocardiographic abnormality and its diagnostic value. Our impression of the discussion is that the majority of speakers did not weigh the diagnostic implications heavily. Cases were cited of ostium primum defects without left axis deviation and of ostium secundum defects with left axis deviation. The discussion touched on the question of electrocardiographic change with increasing age of the patient, the suggestion being that left axis deviation was acquired with progressive left ventricular hypertrophy.

We interject here a repetition of our opinion that such interdependence of left axis deviation and progressive left ventricular hypertrophy is not a basic one. In the same issue of the *British Heart Journal* carrying the discussion mentioned is Hamer's report,[14] in which the vectorcardiogram in atrial septal defect is described and illustrated, with characteristic vectorcardiograms in three of the five clinical cases of atrioventricular cushion defect. Change in the electrocardiogram over the years with the development of pulmonary vascular disease and hypertension has been noted by Campbell and Missen.[6] In our experience such change has not obscured the early vectors that are of diagnostic importance, and characteristic tracings often have been observed to persist from infancy to teen age.

The experience at the Hospital for Sick Children in Toronto, as reported by Evans and his co-workers,[15] parallels ours very closely in that their vectorcardiographic analyses uniformly showed a superiorly oriented frontal loop with vectors rotating counterclockwise or, in a minority, a figure-of-eight pattern about the horizontal line. They had forty-one subjects, categorized as having persistent ostium primum defects, available for study. Three had isolated ostium primum, fourteen ostium primum and cleft mitral valve, eight ostium primum with cleft mitral and tricuspid valves (five of these had some subvalvular communications) and sixteen common atrioventricular canal.

Giraud and his co-workers[16] emphasized the predominant place of the electrocardiogram among the diagnostic elements concerned with defects of the atrioventricular canal. The electrocardiogram, they pointed out, typically shows incomplete right bundle branch block with a mean QRS at $-80°$ to $-115°$ with "levorotation" of the vectors. These authors have presented a clear tabular or semischematic portrayal of the varieties of persistent atrio-

ventricular canal. They have registered potentials from within the ventricles, and view the evidence as favoring the concept of an incomplete bilateral intraventricular block.

Heim de Balsac and his co-workers[17] have discussed the electrocardiographic variations encountered in patients with defects of the atrioventricular canal and have given a correlative dynamic classification as follows:

Group I. Axis deviation −90° to −115°—Right bundle branch block without right ventricular hypertrophy.

Group II. Axis deviation −175° to −135°—Right ventricular systolic overload (right ventricular pressure 45 to 95 mm. Hg).

Group III. Axis deviation −60°—Left ventricular overload (interventricular communication or mitral insufficiency).

Rivier and his co-workers[18] have reported three cases with excellent displays of the vectorcardiogram, and contrast the inconspicuous clinical and roentgenologic features with the typical hemodynamic and electrophysiologic findings. While pointing out the characteristic direction of the QRS loop, they mention that similar records have been obtained of patients with malformations of an entirely different type.

The experience of Kjellberg and his associates[19] led them to the conclusion that it was not possible by electrocardiographic means to distinguish with certainty between an ostium primum defect and other types of atrial septal defect, or between patients with and without mitral regurgitation; but that, if left axis deviation were present, the existence of an ostium primum defect was highly probable. This view is not literally contrary to our own, but our data show a greater correlation of the ostium primum defect and left axis deviation than do the data of their group of twelve cases. In addition, the vectorial analysis of the early electromotive forces may be more important than a calculation of a mean QRS vector.

Sodi-Pallares and his associates,[20] in a discussion of electrocardiography in infants and children, precisely outlined the characteristic features of the electrocardiogram in patients with persistent common atrioventricular canal, the data being similar to those presented in their discussion of thirty-one cases in their experience with a total of 1,331 cases of congenital heart disease.[21] Paul[22] stated that the electrocardiogram has assumed a major role in the diagnosis of endocardial cushion defects, since these are associated with certain uniform and distinctive electrocardiographic features, which constitute a reliable index in the differential diagnosis of ostium primum and ostium secundum atrial septal defects. These observations were based on the records of sixteen patients.

Burch and DePasquale[23] have reported detailed electrocardiographic analyses on one hundred patients with atrial septal defect, ten of whom had the ostium primum variety. Their conclusion, that the electrocardiograms of the septum primum defects differ significantly in a readily recognizable fashion from those of septum secundum defects, in that the former manifest left axis deviation of the QRS or ÂQRS, is in harmony with our view. They state that the differences are so definite as to be of considerable value in the differential diagnosis of the two types of defects, and judge that it would seem most likely that the patterns are related to the relative amounts and to the spatial orientation within the body of the muscle masses of the right and left ventricles. But they neither tie such conjectural differences to the presence of mitral incompetence nor give any theoretic reason for the presence of such differences in the partitioning or arrangement of the myocardial mass. They mention the "irregularity" with which abnormalities of the P wave appear in a group of patients with atrial septal defect. This is in accord with our experience.

It is difficult to assess accurately the diagnostic error that might originate from purely electrocardiographic analysis. We have occasionally observed, however, that a suspected low atrial defect on the basis of a figure-of-eight pattern has proved to be a defect of the usual secundum type, or that a suspected atrioventricular canal deformity with vectorial loops rotating counterclockwise has proved to be a usual type of *ventricular* septal defect. In such cases of ventricular septal defect, the initial QRS vectors have persisted to the 0° to +90° quadrant a considerable time before entering the 0° to −90° quadrant. At one time, a figure-of-eight configuration (or twin-bladed, propeller-shaped loops), oriented either vertically or in a +45° to +225° plane, and found in patients with ventricular septal defects, presented more difficulty of interpretation than it does now, particularly as experience has been gained in the recognition of associated left

ventricular enlargement (or left ventricular volume or diastolic overload).

Case Material

For this study, we reviewed the electrocardiograms of eighty-six patients with defects of the septums in the region of the atrioventricular valves. The classification was: (1) *the partial type*, in which there is no communication below the atrioventricular valve, and (2) *the complete type*, in which there is fusion of the mitral and tricuspid valve tissue across the top of the ventricular septum with small communications underneath, or in which there is a gross ventricular defect below a truly common valve.

At one time, we used the term "transitional type" in reference to fusion of the valves over the top of the septum, but this term has largely been abandoned. In each instance, there was an associated deformity, of varying degree, of the mitral or tricuspid valve, or both. Of the eighty-six patients, twenty-four were judged to have the complete form of the defect. Of these twenty-four, twelve were less than two years of age at the time of operation or postmortem examination. Patients clinically diagnosed as having atrioventricular cushion defect without confirmation by surgeon or anatomist were excluded from this study. A common atrium, in association with a partial form of the atrioventricular canal defect, was found five times.

Difficulties with nomenclature are not entirely solved. For instance, how should one label the rare condition of an atrial septal defect of the usual (secundum) type associated with a cleft mitral valve? And how should one label isolated multiple ventricular septal defects present on the right side under the tricuspid leaflet and mitral valve defects suggesting a congenital anterior (aortic) leaf cleft, but with both septums intact?

The series of cases analyzed in this study includes the group of surgical cases reported in this symposium by Ellis and his associates,[24] as well as the non-surgical cases that had been studied clinically and at postmortem examination and the few atypical or grossly complicated cases that were not included in the surgical study.

Descriptive Features

The cardinal and nearly diagnostic feature of electrocardiograms of patients with low atrial septal defects (so-called ostium primum defects) in association with a cleft atrioventricular valve and complete forms of the common atrioventricular canal is the presence of left axis deviation of the initial or early electromotive forces and, in the frontal vectorcardiogram, a loop that is early oriented in the left axis quadrant; *i.e.*, commonly at an angle of $-30°$ to $-60°$. Many variations occur within the basic diagnostic picture related to the diverse hemodynamic state that may be present in this condition.

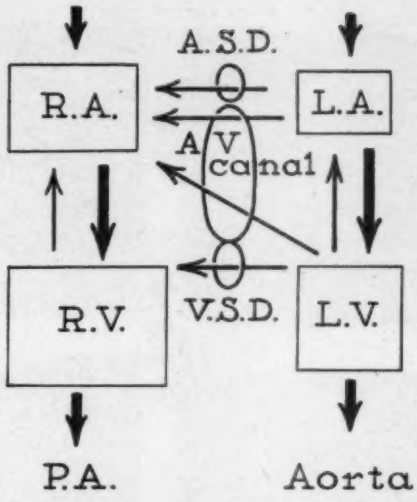


Fig. 1. Schema illustrating the left-to-right shunts and regurgitant flows potentially present in the varied species of the generic atrioventricular cushion group of defects. The right-to-left shunt possible in the presence of a common atrium and pulmonary stenosis or grossly increased pulmonary vascular resistance is not illustrated.

The largest subgroup of patients with nearly diagnostic electrocardiograms were those showing, in scalar leads, a deep or high voltage S wave in leads III and aVF that greatly exceeded the preceding R and was characteristically notched. In this subgroup having the high voltage (greater than 1.5 mv.) notched S in leads III and aVF and no R′ were thirty-two of the eighty-six patients.

Factors Influencing the Electrocardiogram: Following are some of the anatomic and dynamic variables that may influence the electrocardiographic picture (Fig. 1).

(1) The size of the atrial septal defect. This may vary from absence of the septum (cor triloculare biventriculare) to the presence of an intact septum. A dependent variable is a marked difference in size of the atria, with the expectation that when the left atrium is greatly enlarged the atrial septal defect will be relatively small or absent.

(2) Mitral regurgitation. This may vary

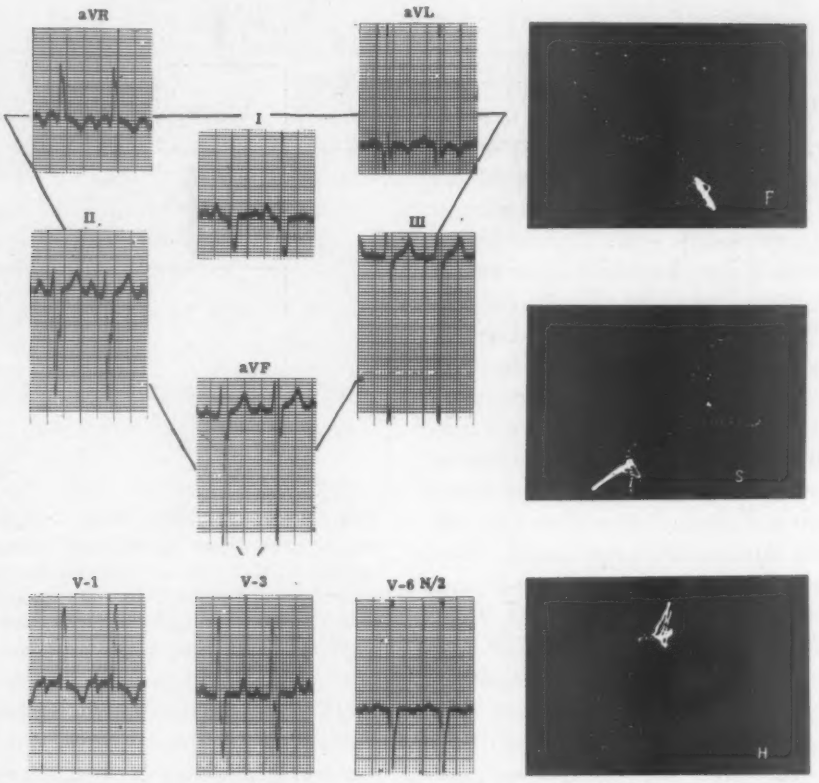


FIG. 2. These electrocardiographic records of a ten year old girl are believed to be nearly pathognomonic of a persistent atrioventricular canal deformity in this age group. There was a complete form of the malformation, with a common atrium and some stenosis of the orifices of the right pulmonary vein. The atrioventricular valve was moderately incompetent. Before repair, the right ventricular pressure was 90 mm. Hg at the time systemic pressure was 100 mm. (surgical and postmortem case).

from being of marked degree to being absent. The regurgitation may often need to be related to the total atrioventricular valve without specifying the mitral, although it is usually the mitral aortic leaflet that is at fault. A tricuspid cleft is of minimal significance. The left ventricular regurgitant volume is frequently directed into the right atrium, but occasionally may be directed into the left atrium. This may contribute to the left atrial enlargement when the interatrial communication is small.

(3) The size of the ventricular septal defect. This defect may be so huge that it creates a functionally single ventricle, or it may be absent and two intact ventricles be present. (In between these extremes are those cases in which there are small interventricular communications below the valves which are fused over the top of the septum.)

(4) Tricuspid regurgitation.

(5) Pulmonary vascular resistance.

(6) Associated defects. The ones that have been observed are: (a) pulmonary stenosis (observed three times), (b) anomalous veins into the right atrium (observed twice) and (c) malalignment of the atrial septum with a separate mitral orifice.

Correlation of Electrocardiographic, Anatomic and Hemodynamic Findings: A correlation between the electrocardiographic picture and the hemodynamics of the central circulation in cases of defects of the atrioventricular canal is difficult to make, except in a crude way, because of the error inherent in assessing the amount of insufficiency of the valve and the total and fractional regurgitation from either ventricle, as well as the error inherent in calculating the relative left-to-right shunt of blood at atrial and ventricular levels. From the dynamic considerations, one should be able to estimate, theoretically, the following electrocardiographic variations:

(1) Evidence of right atrial enlargement in the presence of a large left-to-right transatrial shunt, or a regurgitant flow into the right atrium from either the right or the left ventricle, or from both.

(2) Left atrial enlargement when an atrial septal defect is small or absent and when there is gross mitral insufficiency.

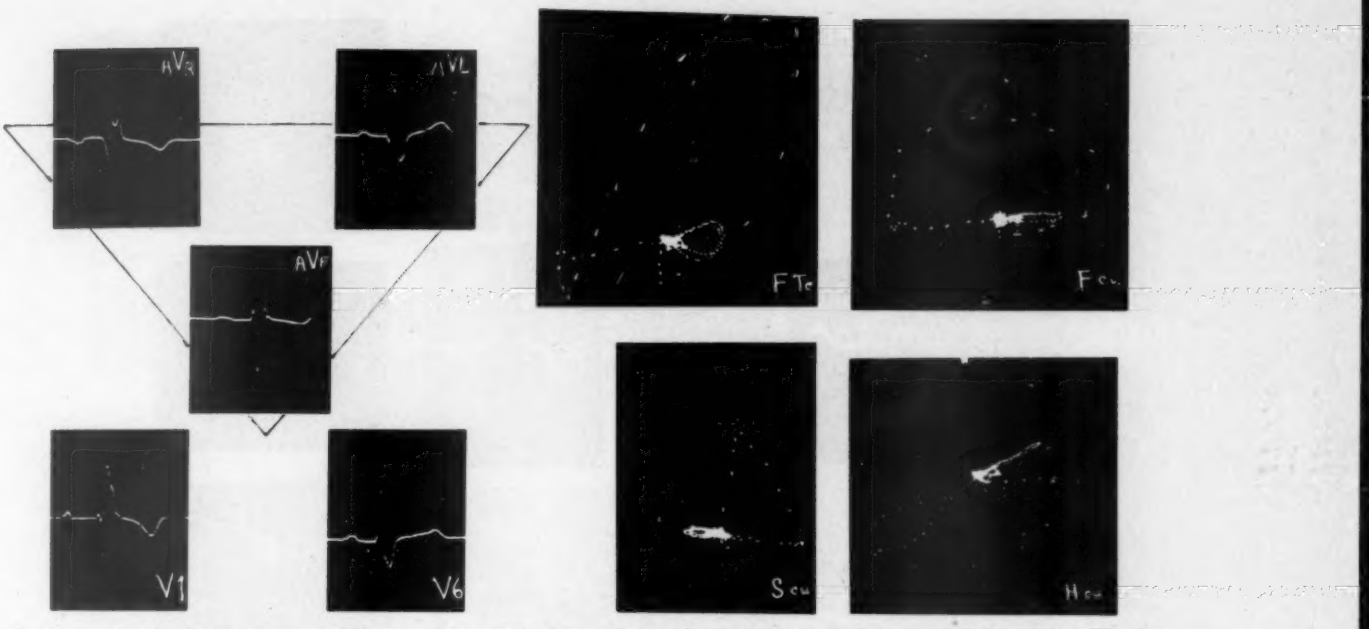


FIG. 3. Records of a fifty-one year old man with a mild form of complete atrioventricular canal deformity. The frequent difference between the frontal vectorcardiogram taken with the tetrahedron system (FTe) and the one taken with the Grishman cube system (Fcu)[27] can be seen: the former is more elongated in the vertical (y) axis. The atrial septal defect was fairly small (2 cm. in diameter) and there were multiple small fenestrations below the valve, constituting the criteria for stating that the defect was of the complete category. Mitral insufficiency was judged to be moderate (grade 2+), but the heart at operation was judged to be only slightly enlarged. Records taken in the operating room at the time of excitation at four points along the anterior interventricular groove, relative to the onset of QRS in the reference lead, showed values of 0.065 (base), 0.035, 0.032 and 0.035 (apex). Those for the posterior surface at varied points were 0.065 to 0.080 second (values within the normal range).

(3) Right ventricular dilatation and hypertrophy related to the left-to-right shunt at either the atrial or ventricular level, or the presence of tricuspid insufficiency, or both. In the presence of a large shunt and an incompetent tricuspid valve, one would expect the picture of a volume (or diastolic) overload of the right ventricle, primarily manifesting itself as an rsR′ type of QRS in the right precordial leads. In the presence of right ventricular systolic hypertension from either an associated pulmonary stenosis, an associated increased pulmonary vascular resistance or a huge ventricular septal defect equalizing systemic and right ventricular pressures, one expects evidence of a pressure loading of the right ventricle with accentuation of the R or R′ in the right precordial leads, along with negativity of the T wave, which may extend into the midprecordial area.

(4) Evidence of left ventricular dilatation or hypertrophy, which will be expressed primarily as volume or diastolic overload brought about by either gross incompetence of the mitral valve or a large shunt from left to right at the ventricular level. A tall QRS and accentuated positive T wave in the left precordial leads are also seen.

The accuracy in predicting the anatomic and hemodynamic situation, as the surgeon will find it, is reasonably good, the greatest errors occurring in estimating right ventricular pressure (or systolic) loading when the complex is primarily of the rsR′ type in the right precordial leads and in estimating the size of the left ventricle. In these areas, there may be a tendency to overestimate the right ventricular systolic pressure or, occasionally, to predict an increased size of the left ventricle when the surgeon can recognize none or very little.

The fact that Toscano-Barboza and his co-workers,[25] in a study of one hundred cases of ordinary atrial septal defect, were unable to establish any close correlation between the hemodynamic findings and the electrocardiogram is pertinent to the problem. One would expect that such relationships in septal defects of the atrioventricular canal type would be even more difficult to establish. These authors also pointed out the not uncommon electrocardiographic feature in patients with atrial septal defect; namely, a q wave in lead V_6 that is present in 35 per cent of patients, approximately half of whom also present an indication of enlargement of the left ventricle.

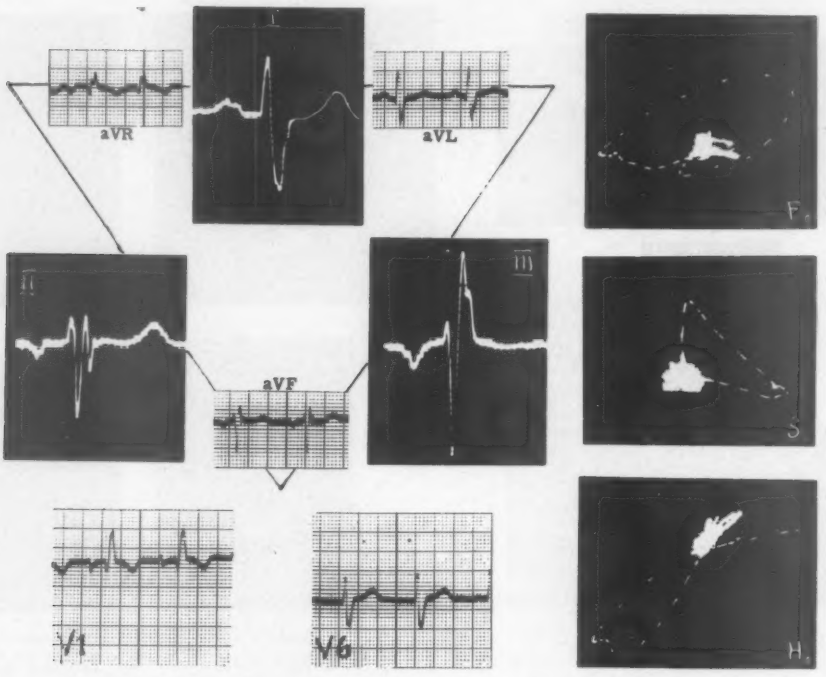


FIG. 4. Electrocardiograms and vectorcardiograms (Grishman cube system[27]) of a forty-eight year old woman with a partial form of common atrioventricular canal deformity and mitral insufficiency, graded slight, at the time of surgical correction of the defect. The right atrium and ventricle were markedly enlarged; left atrium, slightly enlarged; left ventricle, normal; atrial communication, large; and right ventricular systolic pressure before repair, 40 mm. Hg. The three standard leads are augmented; the other scalar leads are taken at normal standardization (1 mv. = 1 cm.). Epicardial records were taken at the time of operation, and the apex and posterolateral surfaces were excited 0.01 to 0.02 second prior to excitation of the anterior basal surfaces (0.03 versus 0.04 to 0.05 second). The surface of the right ventricular outflow tract was excited 0.05 second, and the central area of the right ventricle 0.06 second, after onset of the QRS in the reference lead. The latest areas to be activated were not identified. The QRS was 0.12 second in duration. The QR complex in lead V_1 should be particularly noted, along with the nearly normal right ventricular systolic pressure. The right atrium and ventricle, however, were huge. These records are to be compared with those in Figure 5, in which the hemodynamic situation was equivalent, yet the horizontal vectorial display was markedly dissimilar.

In the group of one hundred cases of ordinary atrial septal defect (ostium secundum type) mentioned, there were seven instances in which the frontal vectorcardiogram showed the QRS loop to be above the isoelectric line, with a counterclockwise sequential rotation of the instantaneous vectors. In six of the seven cases, the frontal vectorcardiogram was of the figure-of-eight configuration.

The additional studies of Toscano-Barboza and DuShane,[26] on electrocardiographic-hemodynamic relationships in ventricular septal defect, are pertinent to this present study and communication, particularly in respect to that group of cases in which there was evidence of right ventricular volume (or diastolic) overloading. In the subgroup of these patients, in which the major defect was a ventricular septal defect, but in which the electrocardiograms showed evidence of volume overloading of the right ventricle, some associated condition was present, such as atrial septal defect, tricuspid insufficiency or anomalous pulmonary veins entering the right atrium.

ANALYSIS OF THE ELECTROCARDIOGRAPHIC FINDINGS

QRS Vectors: It may be emphasized that vectorial analysis reconstructing the vectorial display from the scalar leads, or directly recording the vectorcardiogram, allows one to appreciate the condition present more simply and more rapidly. However, it is not essential in one's diagnostic approach. Much refinement is possible in future vectorcardiographic analyses, and more exact differentiating features are likely to be forthcoming. The important part is the rapid progression of the initial vectors into the left axis quadrant above the isoelectric line, forming a loop that rotates counterclockwise and continues to the right, dependent on a degree of delay in right ventric-

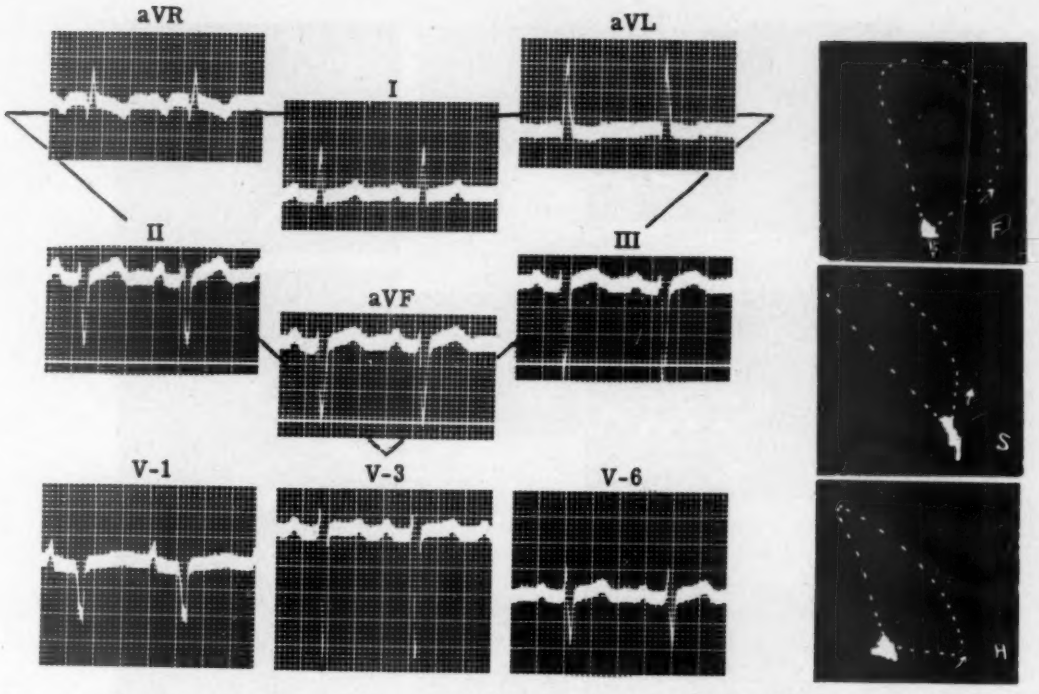


FIG. 5. Electrocardiograms and vectorcardiograms (Grishman cube system[27]) of a sixteen year old patient with a low atrial septal defect (partial atrioventricular canal type). There was no interventricular communication, but there was a cleft mitral valve with only slight (grade 1) insufficiency. A large left-to-right shunt was present at atrial level, and right ventricular systolic pressure before repair was 40 mm. Hg. Attention is directed particularly to the QS complex present in the right precordial lead, despite the large right ventricle.

ular excitation or on right ventricular hypertrophy. The variations may be seen in Figures 2 to 8, inclusive. Attention is directed to the stereotyped electrocardiographic picture, of which Figures 2 and 3 are typical examples. An unusual case wherein all the vectorial forces were of the left ventricular type; *i.e.*, a QS deflection in the right precordial lead (Fig. 5), has special interest, since the large left-to-right shunt was present at the atrial level and the mitral insufficiency was only graded 1 by the surgeon.

In the scalar leads, the characteristic feature is the deep S in leads II, III and aVF. Often there is an rSr′ configuration in the latter two leads and a qR in lead aVL. Correlating with the q in lead aVL are the initial vectors of the frontal vectorcardiogram in the +120° zone.

The figure-of-eight loop, first directed to the right and then to the left about the horizontal line (characteristically categorized in the scalar leads by an rSR′ of relatively low voltage in leads III and aVF), is both less frequent and less valuable, diagnostically, than the broad, open loop oriented superiorly, already described as being nearly pathognomonic of an atrioventricular cushion defect. The type of electrocardiogram does not differentiate between complete and incomplete atrioventricular cushion defect.

To illustrate the difference in electrocardiograms between the patient with an atrioventricular commune type of defect and the patient with a ventricular septal defect, the cases of two sisters may be cited. The one, aged twelve years, who had a ventricular septal defect and moderate pulmonary hypertension, had an electrocardiogram crudely similar to that of her sister, aged eighteen years, who had a partial form of an atrioventricular commune with a large, low atrial septal defect and a mild insufficiency of the mitral valve. The relative left ventricular sizes could be considered equivalent. In the younger girl with the ventricular septal defect, the frontal vectorial display was that of a figure-of-eight double loop, the initial loop being at +40° and the second, more slowly inscribed loop being diametrically opposite in the other quadrant at +225°. The older girl with the atrioventricular commune also had a figure-of-eight type of loop, with an early loop inscribed at −30° and a second at +165°.

P Waves: In patients with mitral insufficiency and a small atrial septal defect of the atrioventricular canal variety, the electrocardio-

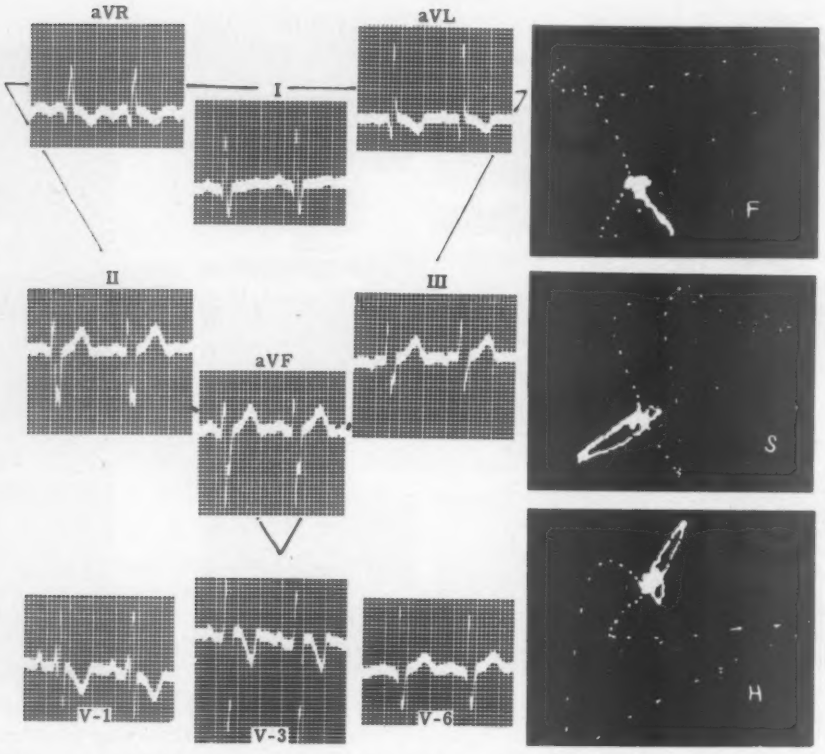


FIG. 6. Records of a four year old boy who had a common atrium and cleft anterior (aortic) mitral leaflet. The mitral insufficiency was moderate (grade 2). Before repair, systolic pressure in the pulmonary artery was 50 mm. Hg, and the aortic systolic pressure was 95. (As in other vectorcardiograms, the modulation inscriptions are at 2.5 msec.)

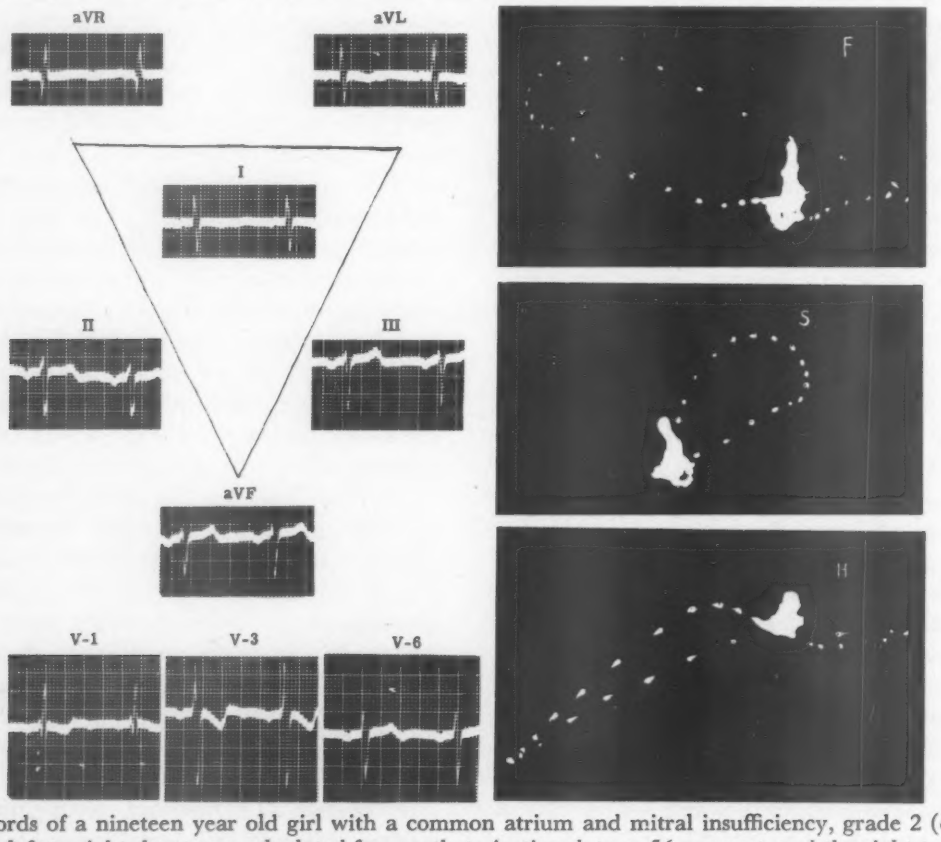


FIG. 7. Records of a nineteen year old girl with a common atrium and mitral insufficiency, grade 2 (on a basis of 1 to 4). The left-to-right shunt was calculated from catheterization data as 56 per cent, and the right-to-left shunt as 44 per cent. Before repair, right ventricular systolic pressure was 75 mm. Hg, and left ventricular pressure, 85 mm.

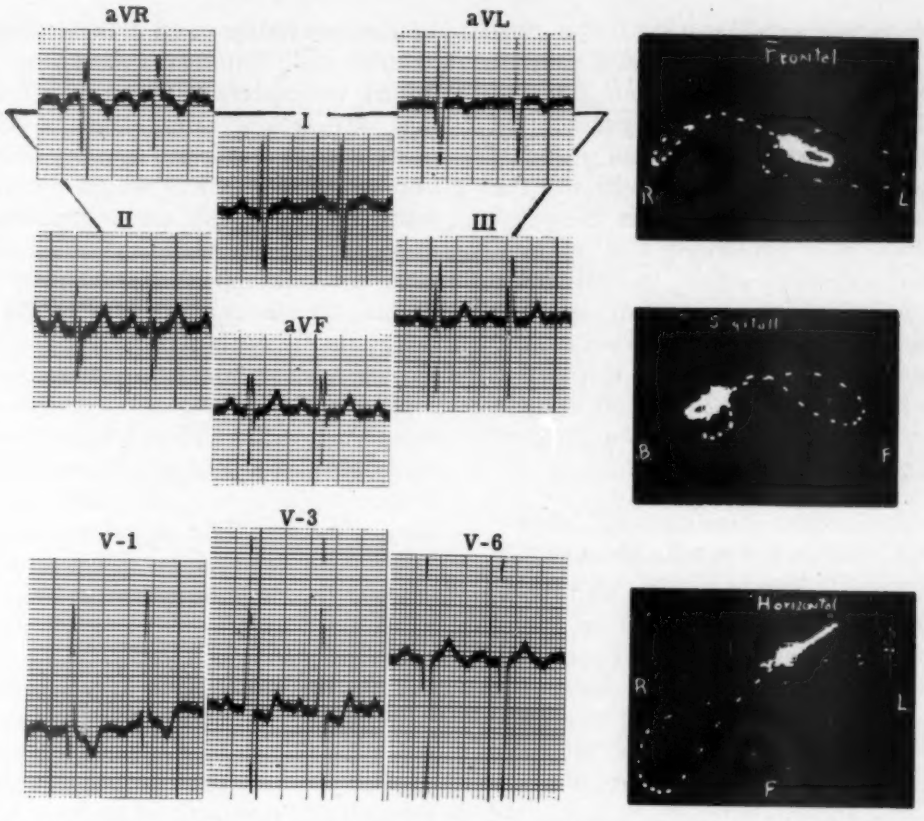


FIG. 8. Records of a five year old boy with a complete form of atrioventricular canal and moderate valvular insufficiency (grade 3). The right ventricle was grossly enlarged, the left moderately so. The right ventricular pressure was 90 mm. Hg, the left 100 mm. It is in this type of record that a single mean axis is not particularly meaningful.

gram may or may not reflect the enlarged left atrium with notched broad P waves in lead I or II, or both, and a marked negative component of a diphasic P wave in the right precordial lead.

In four patients, in whom the surgeon judged no mitral incompetence to be present, the electrocardiograms fitted the diagnosis, having left axis deviation; but the voltage of the QRS was of a lower order.

In answer to the question of how well the electrocardiogram may reflect enlargement of specific chambers, the generalization already made, namely, that from the electrocardiogram the clinician can often predict the dynamic circulatory state and the concomitant relative sizes of the chambers, is as much of a conclusion as this study permits. In some cases, very typical "P mitrale" waves may be seen, with rather wide notched P waves and a diphasic configuration in the right precordial area. While, in certain instances, these have fitted well with a recognized left atrial enlargement, the correlation has not been uniform. The same conclusion pertains to the high voltage, peaked P waves in leads II and III and in the right precordial leads, as evidence of right atrial enlargement, in that these are frequently present but may not always be so.

Q Wave in Lead V_6: Of our group of eighty-six patients, 70 per cent had a Q wave in lead V_6, in contrast to 35 per cent of the one hundred cases of ordinary atrial septal defect studied by Toscano-Barboza and his co-workers.[25] This leads to the conclusion that a Q wave in lead V_6, *per se*, is twice as likely to be present in defects of the atrioventricular canal type and that the discriminatory value might be further augmented if, from a group of cases of ordinary atrial septal defect (ostium secundum), one should exclude those in which clinically recognized conditions are causing an increased load on the left ventricle (*e.g.*, systemic hypertension) and if, with the same group of cases, one should make technically certain that the electrode is correctly placed in the 6 position.

Prolonged P-R Intervals: An additional feature that is frequently present in the electrocardiograms of patients with defects in the

region of the atrioventricular canal is a prolonged P-R interval, this sign being present in approximately 60 per cent of our patients as compared to approximately 15 per cent of patients with ordinary atrial septal defect.[20] In the group of patients with deformities in the region of the atrioventricular valve, the presence or absence of a prolonged P-R interval has no discriminatory value in indicating whether the defect is of the partial or complete variety. The P-R interval is not necessarily a fixed feature. Thus, we found it to shorten, in one case, from 0.26 to 0.20 second and, in another, from 0.20 to 0.16 second in a few days following surgical treatment.

The Basic Congenital Aberration Underlying the Unusual Electrocardiogram

Our hypothesis is that the basic electrocardiographic abnormality is related to an anomalous left bundle branch system. Recordings of potentials from the cavities and surfaces of the ventricles made at the time of operation have given support to such a thesis, although this study is not completed. The method, which involves a limited survey of the epicardial surface, has serious limitations both in regard to the number of points that may be recorded and, in our system, in regard to the fact that only one point at a time is recorded along with a reference lead.* It seems possible that this approach will not give a conclusive and definitive answer, but certain statements seem valid.

The potentials from the right and left ventricular cavities have been of the normal configuration for the respective cavity; this would be strong evidence against there being a partial left bundle branch block. Similar records of cavity potentials have been recorded by Giraud and his co-workers.[16] In our work, preselected epicardial reference points were used at first. They revealed that the posterior and lateral epicardial surfaces were excited at a normal time. It was noted that early or immediate excitation of the epicardium in the anterior interventricular groove was not as uniformly present as it was reported to be in the literature[28,29] and as it was seen by us in control cases. Further detailed exploration in two recent cases has revealed no early excitation (*i.e.*, within 0.000 to 0.005 second after onset of QRS in the reference lead) of this area. This would fit into the theory that early left ventricular forces could be related to the advancing excitation front in the posterolateral wall of the ventricle, with the usual early balancing excitation front in the anterior wall being lacking because of delay and irregularity of its plane. It should be emphasized that the preliminary data are inadequate to prove this concept. Our contemporary theory offered herein, for the secret of the displayed unusual mean cardiac vectors, is the possibility of a different orientation of the advancing fronts of depolarization dependent upon congenital absence of a portion of the left bundle branch system.

* A twin-beam Sanborn electrocardiograph was used in the surgical theater, a peripheral limb lead being employed as reference. The exploring electrode was at first a unipolar one, but later proximity electrodes 1 mm. apart, set in a plastic head 5 mm. in diameter, were used. With a paper speed of 50 mm. per second, the minimal time interval that was reasonable to measure was 0.005 second.

Comment

The question arises as to whether it is possible to reconcile the conflicting opinions regarding the authenticity of a specific electrophysiologic aberration in defects of the lower atrial septum (generically grouped as atrioventricular cushion anomalies) and the importance of the role played by mitral incompetence. It would appear that those investigators with a fairly large number of patients support the view that the conduction defect is characteristic of the lower atrial defect, while those with fewer cases, even though they are observers of renown in the field of congenital heart defects, do not endorse it. This hardly explains the discrepancy; but if the latter group should accent that part of their experience wherein patients with ordinary atrial septal defect, ventricular septal defect, patent ductus or combined lesions have left axis deviation, it would dilute the importance of such electrocardiographic features as being of diagnostic validity in their patients with defects of the atrioventricular cushion type.

As the inquisition is turned toward ourselves, the question arises whether prejudice or conviction has led us to ignore the records that are contrary to our view. It is true that we have sent a few patients to operation with the diagnosis of probable or possible atrioventricular cushion defect only to have the surgeon find an "ordinary type" of atrial or ventricular septal defect (or both). On the other hand, however, in the past three years, we have not sent to operation a patient with the diagnosis of

ordinary atrial septal defect (ostium secundum) who did not have this lesion.

It should be understood that, in rare instances, the electrocardiograms of other congenital defects, such as tricuspid atresia, may have a roughly similar form. We have encountered only one patient whose electrocardiogram was entirely characteristic of the atrioventricular cushion defect (the QRS loop in the frontal plane being completely above the isoelectric point) who was found at operation to have a ventricular septal defect. The surgeon noted that the defect probably extended backward more than usual, but the case would have to be categorized as that of an ordinary ventricular septal defect.

Emphasis should be placed upon the exceptions to any diagnostic axiom, and the medical literature already quoted indicates that the relation of the described left axis deviation and vectorial display to defects of the atrioventricular cushion type is not an absolute one. It is interesting to note that we have encountered so few exceptions, and we would submit that the relationship is a phenomenal and established one.

Summary

The electrocardiogram is the most important single item in alerting the physician to the diagnosis of congenital cardiac anomalies stemming from defective formation of the atrioventricular canal. It is characterized by left axis deviation with the early manifest frontal vector characteristically in the 0° to −60° zone. The tracings usually show evidence of enlargement of the right ventricle, particularly an rSR configuration in right precordial leads, the picture of volume overloading of the right ventricle. Different hemodynamic profiles (for instance, the amount of shunting at the atrial and ventricular levels, the degree of mitral insufficiency and the pulmonary hypertensive level) will be additively reflected in the basic electrocardiographic pattern. The typical electrocardiogram may be encountered occasionally in other types of congenital heart disease, particularly ventricular septal defects located posteriorly under the septal tricuspid leaflet. It is believed that the electrocardiographic pattern is related to a congenital aberration of the left bundle branch system.

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Differential Diagnosis Between Persistent Atrioventricular Canal and the Combination of Atrial and Ventricular Septal Defects*

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We have been impressed by the frequency with which two different types of anatomic patterns give rise to similar clinical, hemodynamic and electrocardiographic findings. Several examples may be cited: A high ventricular septal defect with aortic regurgitation may simulate patent ductus arteriosus,[1,2] transposition of the great vessels with pulmonary stenosis may simulate tetralogy of Fallot[3] and the combination of atrial and ventricular septal defects may be confused with true persistent A-V canal. This is the subject of the following presentation. Our observations are based on studies of nine patients with combined atrial and ventricular septal defects and five patients with persistent A-V canal. In the group with combined septal defects, the diagnosis was confirmed at autopsy in three cases and at surgery in one. In the remaining five cases, the diagnosis was suggested by the data obtained by cardiac catheterization and angiocardiography. In the second group with persistent A-V canal, the diagnosis was proved at autopsy in three cases and at surgery in two.

Anatomy

There is great anatomic difference between the combination of auricular septal defect and ventricular septal defect (ASD plus VSD) and persistent A-V canal. Three autopsy specimens showing combined septal defects, which we have studied, show widely patent foramina ovalii (Fig. 1) at the auricular level. Extensive reabsorption of the septum primum and incomplete development of the septum secundum account for this patency. This defect should probably not be designated as the "secundum" type, as currently used. An ostium secundum is a rare malformation. Its abnormal patency after birth is unusual and it is located at a high level of the auricular septum,[4] near the superior vena cava (Fig. 2).

The ventricular septal defect is of the middle basal type;[5] i.e., the one currently described (and adequately so) as the membranous type of ventricular septal defect. In persistent A-V canal, failure of the dorsal and ventral cushions of the primitive A-V canal to meet in the midline is responsible for the low type of atrial septal defect (ostium primum), together with a posterior basal ventricular septal defect (Fig. 2). The degree of separation between the dorsal and ventral cushions will determine the size of the A-V canal. The smallest size would correspond to the so-called incomplete form of A-V canal,[6] which is an ostium primum with minimal, if any, ventricular septal defect and mitral regurgitation. The higher position of the internal leaflet of this cleft valve is responsible for this behavior.

Physiopathology

In ASD plus VSD, as far as we have been able to ascertain, there is passage of arterial blood from left to right at both the auricular and ventricular levels. This causes a variable amount of increased flow through the lungs and hypertension in the lesser circuit. Although this hypertension may be slight, some subjects may show considerable elevation of pressure. On occasion a mixed shunt may take place with resulting slight peripheral arterial unsaturation. In persistent A-V canal, especially the complete form, which is the one more easily confused with

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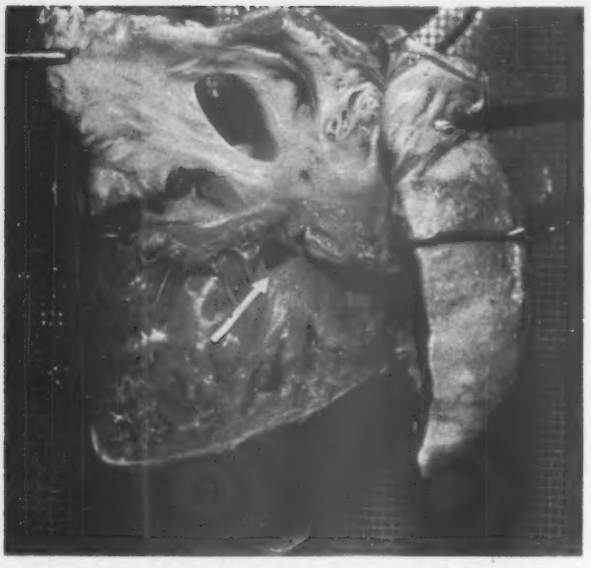


FIG. 1. Case 1. The heart of a ten year old girl on whom surgery was attempted for closure of the atrial septal defect. The atrial defect was a widely patent foramen ovale. The ventricular septal defect, indicated by the arrow, was a "membranous" type of defect, just slightly covered by the septal leaflet of the tricuspid valve.

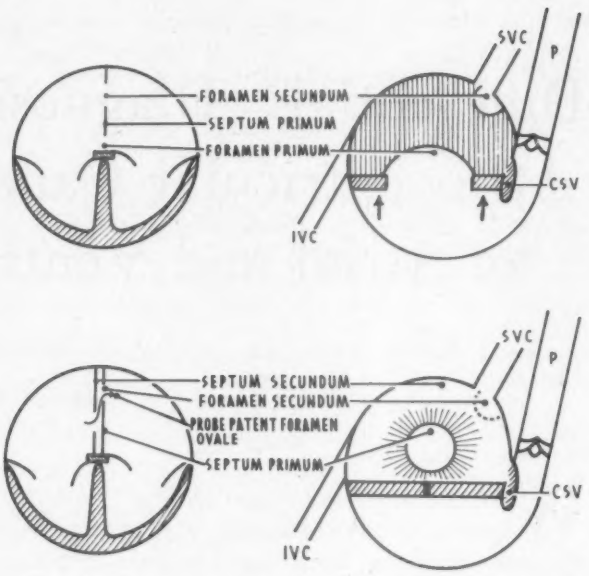


FIG. 2. Diagram which illustrates two stages in the embryological development of the atrial septums. The upper figures show a stage which demonstrates the presence of an ostium primum, when the dorsal and ventral cushions of the atrioventricular canal (indicated by the arrows) have not met in the middle. In the lower figure, these cushions have come in close contact and the foramen primum has been occluded. Note, in the upper figure, that the foramen secundum is still patent.

the condition under discussion, a left-to-right shunt is always present. Here, too, hypertension develops in the right side of the heart, with the not uncommon possibility of a right-to-left shunt.[7,9]

CLINICAL FINDINGS

The diagnosis of a congenital malformation associated with increased pulmonary flow may be suggested by a past history of repeated respiratory infections and physical underdevelopment. More important are the physical findings which suggest that, in addition to ventricular septal defect, an atrial septal defect is present. Signs consistent with pulmonary hypertension are usually present, including accentuated second pulmonary sound. While one is justified in diagnosing a ventricular septal defect on the basis of a harsh systolic murmur and thrill over the lower left sternal margin, doubt arises when the same murmur, or perhaps a different murmur, is heard higher, at the

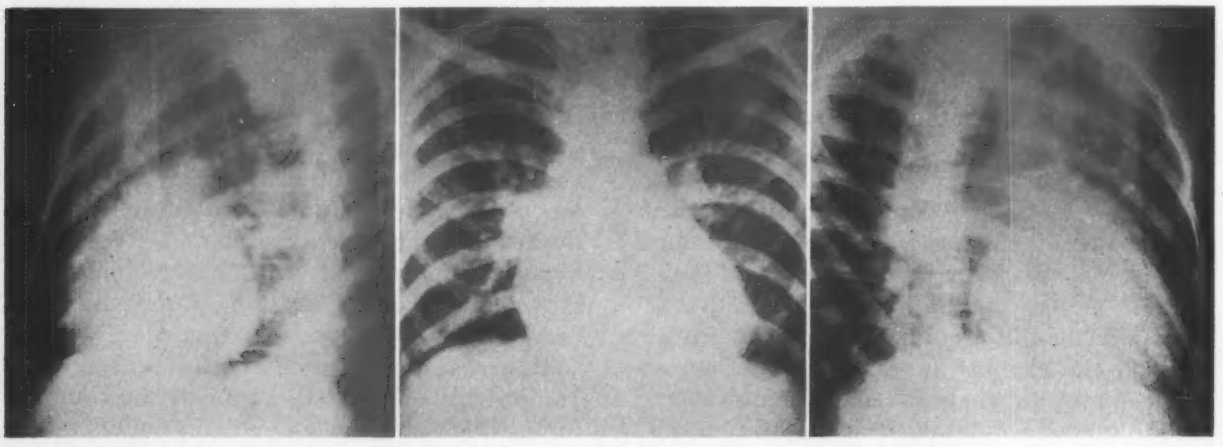


FIG. 3. Case 8. Teleoroentgenograms (left-oblique, posteroanterior and right-oblique views) of a proved case of combined atrial and ventricular septal defects. In addition to the right-sided enlargement and the profuse vascularity of the lungs, note the suggestion of left atrial and ventricular enlargement.

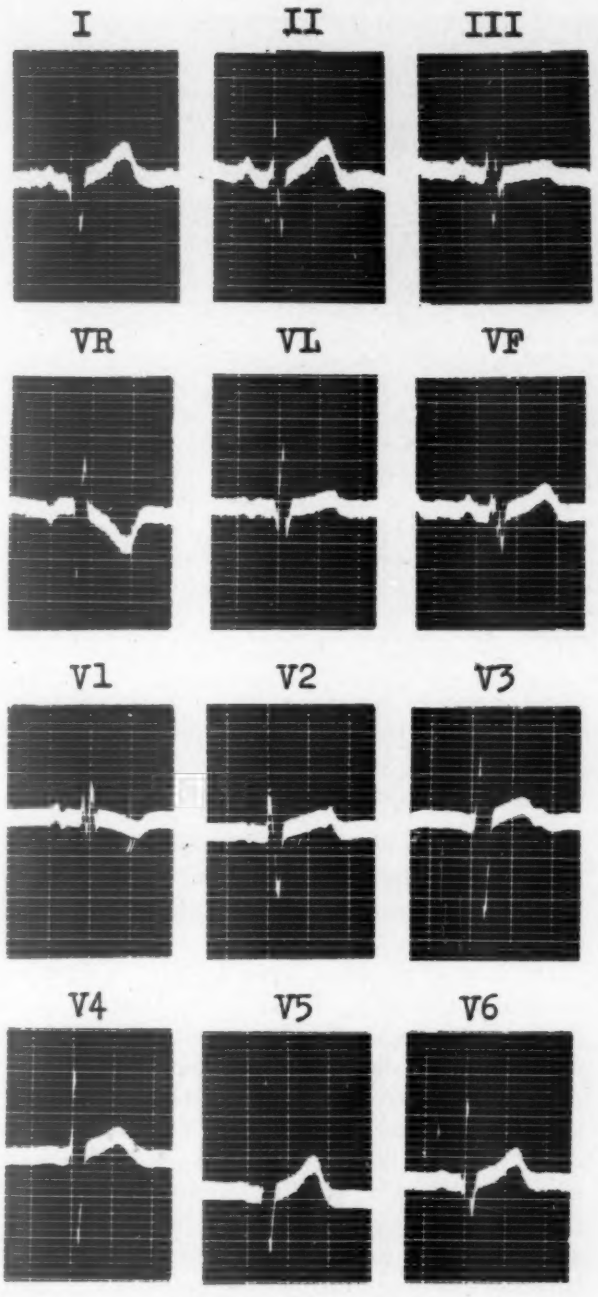


FIG. 4. Case 4. Electrocardiogram of one of the patients suspected of having atrial and ventricular septal defects. The atrial defect was repaired surgically. The outstanding features of this tracing are the left axis deviation, the incomplete right bundle branch block (RSR′ in lead V_1) and suggestive signs of both right and left ventricular enlargement.

second left intercostal space, and particularly when the second pulmonary sound is constantly and widely split. In our experience, this would suggest the additional presence of an atrial septal defect rather than isolated ventricular septal defect. In reviewing our material, we note that, on purely clinical grounds, we have been more prone to make the diagnosis of ventricular septal defect, but in half the cases, the presence of an added atrial septal defect was suspected.

X-RAY FINDINGS

Radiologically, the picture is usually consistent with the diagnosis of a malformation which causes more or less marked left-to-right shunt, expressed by enlargement of the right cardiac chambers, the pulmonary artery and the hilar vessels. Because this combination of malformations is difficult to diagnose, one is forced to suspect the diagnosis by elimination. Should the x-ray picture be suggestive of an atrial septal defect, one can almost certainly rule this out as the only diagnosis because there is enlargement of the left cardiac chambers, which is more consistent with the diagnosis of ventricular septal defect. This diagnosis cannot be clearly differentiated from persistent A-V canal (Figs. 3 and 8).

ELECTROCARDIOGRAPHY

Electrocardiograms provide a most interesting clue. They show the features classically described for atrial septal defect; namely, a partial right bundle branch block (RSR′ in lead V_1) and suggestive evidence of right ventricular hypertrophy. Features commonly seen in ventricular septal defect are also present, particularly those expressing biventricular hypertrophy. It can only be suspected that the defect is, in all probability, not isolated, but either a persistent A-V canal or a combination of ASD plus VSD. In other words, there is the association of the following helpful data: (1) left axis deviation with a polyphasic complex in lead III, (2) right bundle branch block and (3) signs of either left atrial or left ventricular enlargement, but usually both (Fig. 4).

HEMODYNAMIC FINDINGS

Cardiac catheterization studies have given us valuable information, as may be seen from the data in Table I.

Gas analysis data, suggestive of the diagnosis under discussion, show a first step-up of oxygen content at the atrial level of 2 to 3 volumes per cent and a second step-up of variable magnitude at the ventricular level. In our cases, first oxygen step-up varied from 1.97 to 3.12 volumes per cent. The second step-up, when high, is a reliable sign. It was present in five subjects in whom it ranged between 1.05 and 2

TABLE I
Hemodynamic Data in Combined Atrial and Ventricular Septal Defects

Case No.	Age (yr.)	Gas Analysis O2 Content (vol. %)						Pressures (mm. Hg)			Pulmonary Flow (L./min.)	Diagnosis
		SVC	RA	RV	PA	LA	BA	RV	PA	BA or LV		
1	10	8.55	11.25	12.30	11.90	13.90	13.50 (86.3%)	89/4.2	90/49	101/67	11.88	Autopsy and catheterization
2	6	11.75	14.05	15.96	15.50	...	18.7 (98.4%)	31/1	29/79	...	3.6	Angiocardiography
3	5	7.99	9.96	11.95	11.95	...	12.36 (97.2%)	35/2.4	28/7.1	61/39	5.4	...
4	9	9.15	12.27	12.82	12.65	12.40	14.27 (90.8%)	49/1.9	33/9.6	108/2.7	15.2	Operation
5	35	13.25	15.43	15.73	16.55	15.70	15.94 (96.5%)	40/0.6	33/15	...	21.0	Angiocardiography
6	14	11.98	14.56	16.03	15.60	...	16.47 (96.5%)	76/4	72/41	93/67	...	...
7	12	10.22	12.44	14.44	14.72	15.65	15.68 (82.4%)	80/4	78/42	100/12	14.5	...
8	18	...	...	...	...	...	...	...	...	...	...	Autopsy
9	1 mo.	...	...	...	...	...	...	...	...	...	...	Autopsy

NOTE: SVC = superior vena cava. RA = right atrium. RV = right ventricle. PA = pulmonary artery. LA = left atrium. BA = brachial artery. LV = left ventricle.

volumes per cent. In the other two subjects, the step-up was minimal.

Right ventricular pressure: It has been our experience that an atrial septal defect does not usually produce a marked elevation of right ventricular pressure. While some subjects have slight pressure elevation, those with readings above 70 mm. Hg should be suspected of having a complicated atrial septal defect, as seen in three of our subjects (Cases 1, 6 and 7).

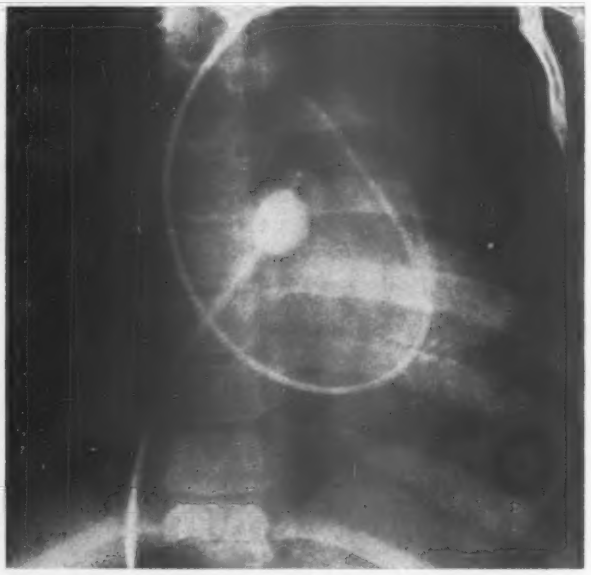


FIG. 5. Case 1. X-ray film taken during catheterization of the patient depicted in Figure 1. One catheter entered the heart from the saphenous vein (Dotter-Lukas catheter); its balloon is in the left auricle and it occludes the atrial septal defect. The second catheter entered from the left arm into the superior vena cava, right atrium, right ventricle and pulmonary artery. The second catheter (double exposed) detected a left-to-right shunt at the ventricular level, thus suggesting the diagnosis of a ventricular septal defect.

SPECIALIZED TESTS DURING CATHETERIZATION

Several specialized tests during cardiac catheterization may aid in the diagnosis of this condition:

Occlusion of the Atrial Septal Defect: This may be attempted (Fig. 5) with the Dotter-Lukas catheter[8] while another catheter is introduced simultaneously into the right ventricle. This second catheter will detect a left-to-right shunt at the ventricular level. While this test may be of aid in the diagnosis, there are several possible causes for error: (1) The second left-to-right shunt may be produced by the presence of an anomalous pulmonary venous connection, which becomes evident at the ventricular level although beginning at the atrial level. This, incidentally, was the interpretation erroneously given in one of our cases proved at autopsy (Case 1). (2) A second shunt is also possible at the ventricular level in cases of persistent A-V canal.

Passage of Catheter through a Ventricular Septal Defect: In favor of persistent A-V canal, and against the diagnosis of ASD plus VSD, is the passage of the catheter from the left to the right ventricle.[9] This is possible by introducing the catheter into the left atrium through the atrial septal defect, from where it is pushed into the left ventricle. Pull-out pressure recordings show the high left ventricular pressure, the moderately

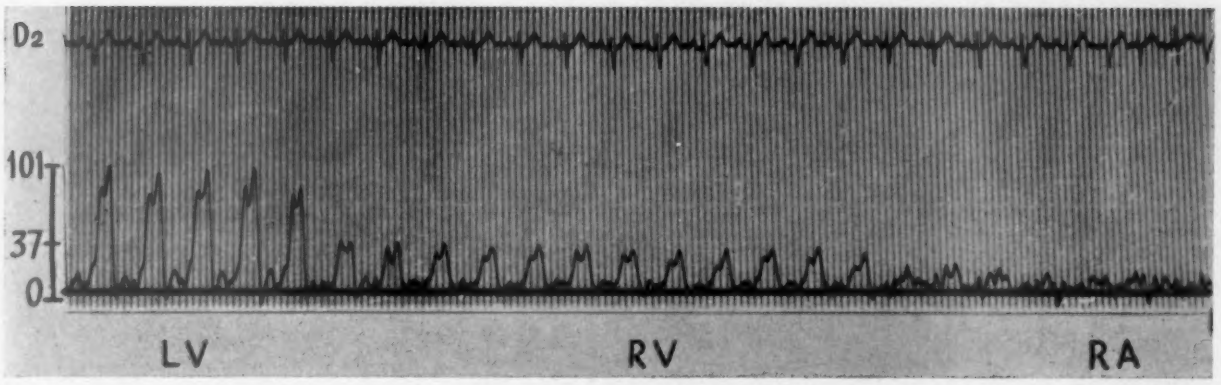


FIG. 6. Case 5. Continuous pressure record of the patient depicted in Figure 8. The pull-out tracing (below) seems to indicate that the catheter was easily withdrawn from the left ventricle (LV) into the right ventricle (RV) before entering the right auricle (RA). This sequence of events is suggestive of the diagnosis of persistent A-V canal. D2 = lead II.

elevated right ventricular pressure and, finally, the right atrial pressure (Fig. 6).

Selective Angiocardiography: This method may prove to be a useful means of solving the problem. In one of our subjects, the opaque substance was injected into the right auricle. Films were taken at half-second intervals. The first of a series of eight films shows the left ventricle filled and a gradual refilling of the right ventricle (Fig. 7).

ILLUSTRATIVE CASE REPORT

The following case illustrates the diagnostic difficulties between these two conditions.

CASE 5. O. G. was a thirty-five year old man who complained of moderate dyspnea on effort and palpitation. Physical examination revealed the cardiac apex to be at the fifth left intercostal space, somewhat to the left of the mid-clavicular line. A coarse systolic thrill was felt at the fourth and fifth left intercostal spaces and a harsh grade 3 systolic murmur was heard at the same site. The second pulmonary sound was accentuated and split. The diagnosis of ventricular septal defect was postulated clinically. Because of the wide splitting of the second pulmonic sound, the possibility of an added malformation was entertained.

X-ray examination revealed slight-to-moderate cardiomegaly, with slight prominence of the pulmonary segment and increased lung vascularity (Fig. 8). There was questionable enlargement of the left atrium and minimal enlargement of the right ventricle. The electrocardiogram revealed left axis deviation, partial right bundle branch block and suggestive signs of left ventricular enlargement (Fig. 9). These findings were suggestive of the diagnosis of persistent A-V canal.[10]

Catheterization was performed with the following results (see Table I for abbreviations):

	Oxygen Contents (vol. %)		Pressures (mm. Hg)
SVC	13.25		
RA	15.43		
RV	15.73		40/6
PA	16.55		33/15 (24)
LA	15.70		(5)
LV	15.94	(96%)	84/7 (31)
BA			102/56 (71)

It was in this case that a continuous pressure tracing was recorded as the catheter was withdrawn from the left ventricle into the right ventricle and then into the right auricle (Fig. 6). This peculiar morphology seems to be an important diagnostic sign in persistent A-V canal.[9]

Angiocardiography of this case may be summarized as follows: The opaque substance was injected directly into the left ventricle, where the catheter was placed after passing through an atrial septal defect (Fig. 8). Films were taken at half-second intervals. The opaque substance was visualized in the pulmonary artery at the end of the injection. Film 2 (Fig. 8, lower right) shows passage of opaque substance from left to right in the form of a jet. The other films show gradually progressive filling of the right ventricle and pulmonary vascular network. This angiocardiogram was highly suggestive of the presence of a ventricular septal defect with a left-to-right shunt. Yet one is forced to admit that, despite the appearance of a jet-like stream of opaque substance between the left and right ventricles, it is practically impossible to decide whether this is an isolated ventricular septal defect or if it is the ventricular part of a large persistent A-V canal. Against the latter diagnosis is the failure of the left atrium to fill from the left ventricle in a retrograde fashion. However, this is not a deciding element. It would only

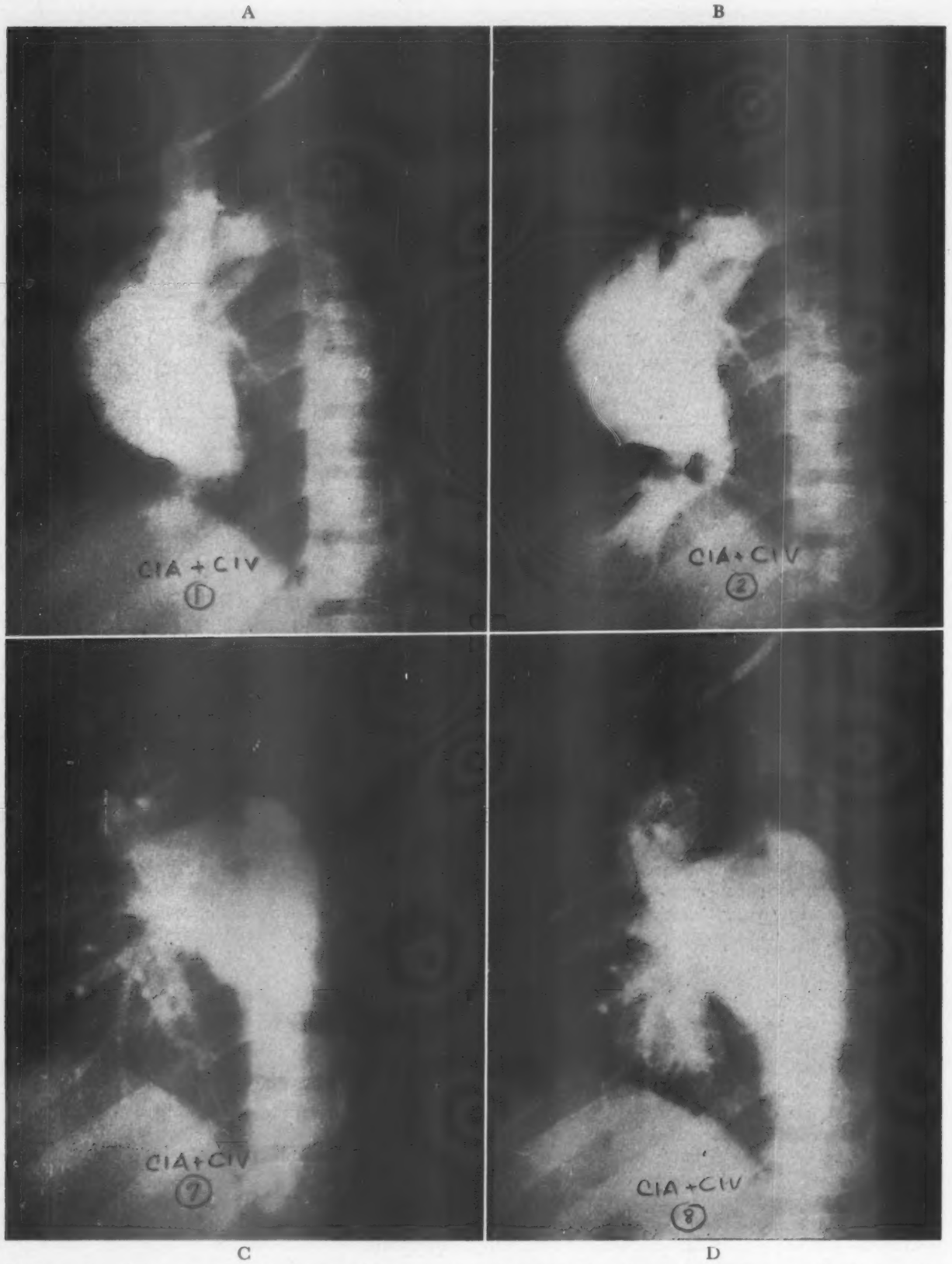


FIG. 7. Case 2. A conventional angiocardiogram obtained by injecting the opaque substance directly into the superior vena cava. In this case an atrial septal defect was entered with the catheter. The angiocardiogram seems to demonstrate an added ventricular septal defect because the last two films (7 and 8) show filling of the right ventricle from the left ventricle. A and B are films 1 and 2, C and D are films 7 and 8.

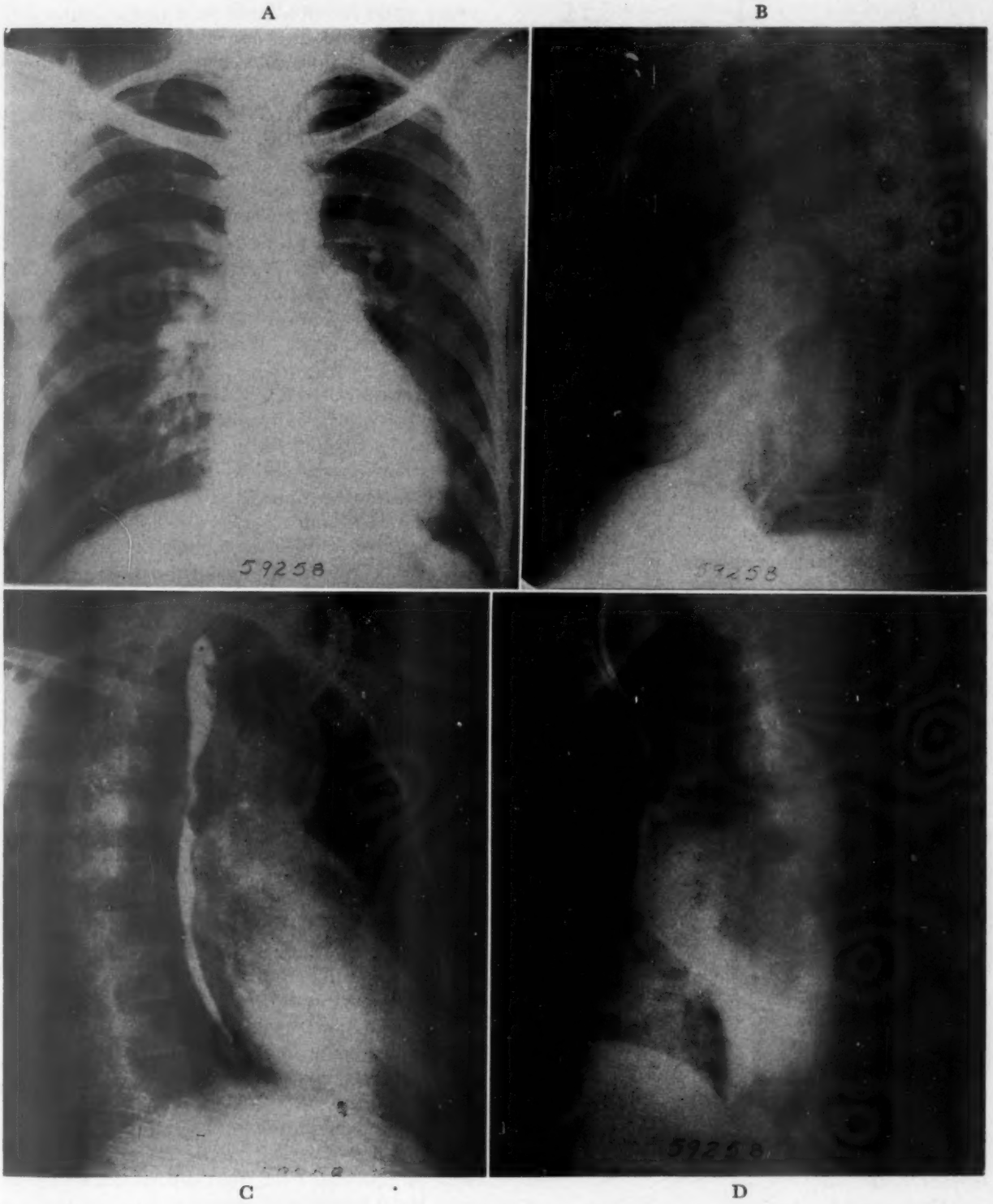


FIG. 8. Case 5. Teleoroentgenogram and angiocardiogram of a thirty-five year old patient in whom the final diagnosis is still in doubt since elements of persistent A-V canal, as well as of the combination of atrial and ventricular septal defects, are present. A, B and C are the posteroanterior, left-oblique and right-oblique teleoroentgenograms. Note the relative smallness of the heart with profuse vascularity of the lungs. Left-sided enlargement is not apparent. D is film 2 of the angiocardiogram taken with the catheter in the left ventricle. The septum is clearly visualized, the pulmonary artery is seen faintly filled with opaque substance and, just below the origin of the aorta, a stream of opaque substance is seen to enter the right ventricle. This is good evidence of a left-to-right shunt but it is difficult to decide whether it is an isolated ventricular septal defect or a persistent A-V canal. The fact that the left atrium did not fill from the left ventricle would perhaps cast some doubt on the latter diagnosis.

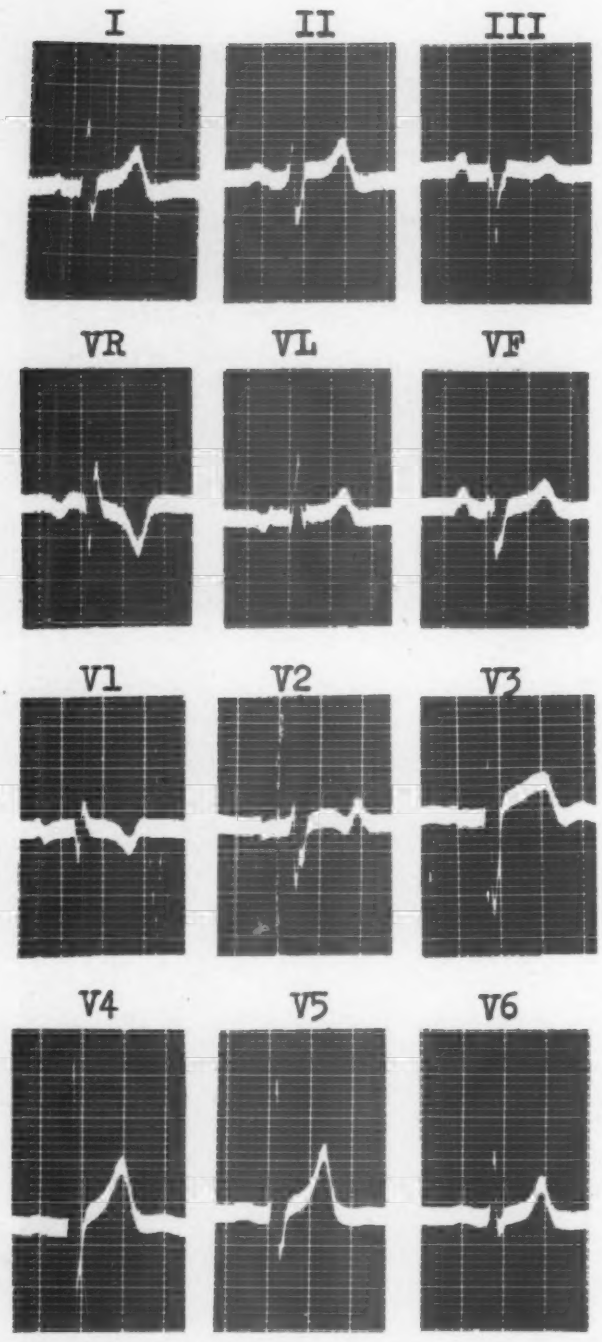


FIG. 9. Case 5. Electrocardiogram of the patient depicted in Figure 8. Note the left axis deviation, the partial right bundle branch block and the suggestive signs of left ventricular enlargement, i.e., tall peaked T wave in leads V_5 and V_6.

mean that if the lesion is an A-V canal, there is no demonstrable mitral regurgitation.[11]

COMMENT ON SURGERY

The diagnosis of isolated atrial septal defect, if a given case is found operable, is followed by a relatively simple and curative operation. However, when an associated ventricular septal defect is suspected, either in the isolated form or as one of the anatomical components of persistent A-V canal, surgery, if justified, is certainly a more risky procedure requiring a difficult open heart technic.

The need for an accurate diagnosis may be illustrated by our brief surgical experience with two subjects. One of them (Case 1), a ten year old girl, was operated on with the diagnosis of atrial septal defect, "possibly of the ostium primum type." Technical difficulties and the development of a severe arrhythmia made it impossible to attempt surgical closure of the atrial septal defect (Fig. 1). The patient made a poor recovery and died a few days later with a severe pericarditis. It is obvious that if the atrial septal defect had been successfully operated upon, there would still have been the problem of the ventricular septal defect. The second patient (Case 4) was a nine year old girl in whom the tentative clinical diagnosis was ventricular septal defect, possibly associated with an atrial septal defect. Catheterization proved the presence of an atrial septal defect. This was successfully repaired. However, the child still has a loud harsh systolic murmur over the midprecordial area and still has, as she did preoperatively, left-sided cardiac overloading, which cannot be attributed solely to the atrial septal defect (Fig. 4). For this reason, it is believed that she has an added ventricular septal defect.

SUMMARY AND CONCLUSIONS

A series of nine subjects with the combination of ASD plus VSD and five subjects with A-V canal were studied. The differential diagnosis between these two conditions poses a difficult problem, since both have quite similar clinical, radiological and electrocardiographic features. Both have some degree of right-sided and left-sided cardiac overloading. Clinically, the suspicion of either of these conditions as opposed to isolated atrial septal defect or isolated ventricular septal defect is based on the presence of a low systolic murmur over the third to the fourth or fifth left intercostal spaces. In addition, a systolic murmur is commonly heard at the pulmonary area and the second pulmonary sound is both loud and split.

Radiologically, right-sided cardiac enlargement, increased vascular markings and a suggestion of left auricular and/or left ventricular enlargement leads to the belief that atrial septal

defect and ventricular septal defect, either combined or forming part of a single entity (persistent A-V canal), are present.

Electrocardiographically, left axis deviation in the presence of partial right bundle branch block and signs of biventricular hypertrophy suggest either diagnosis.

Specialized studies aid in the differential diagnosis but these, too, have some limitations. The most useful have proved to be:

1. Catheterization, when the following data are present: (a) a left-to-right shunt at the auricular level; (b) another signifícant left-to-right shunt at the ventricular level; (c) the passage of the catheter through an atrial septal defect into the left auricle in a high position (these findings were present in seven cases); (d) the direct passage of the catheter from the left to the right ventricle would be suggestive of persistent A-V canal, when the left ventricle is entered from an atrial septal defect; (e) occlusion of the atrial septal defect with a Dotter-Lukas catheter would allow another catheter, simultaneously placed in the right ventricle, to detect a left-to-right shunt at the ventricular level (this method confirmed the diagnosis in one of our autopsy subjects, Case 1).

2. Angiocardiography. The injection of opaque substance directly into the left ventricle should give early filling of the right ventricle through a ventricular septal defect, as in Cases 2 and 5, and may show the site and size of the defect. Mitral regurgitation during this procedure, i.e., early filling of the left atrium from the left ventricle, would be more in favor of persistent A-V canal than of combined atrial and ventricular septal defects.

Acknowledgment

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Surgical Management of Persistent Common Atrioventricular Canal*

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Classification of congenital heart defects on the basis of detailed anatomy has been greatly stimulated by recent progress in open heart surgery. The anatomy of interatrial communications, which constitute one of the common varieties of congenital heart lesions, has been re-emphasized in recent years and valuable contributions toward the accurate clinical diagnosis of these lesions have been made. Since surgical treatment is available for nearly all varieties of these lesions, the practical importance of their identification is evident.

Classification

A classification of interatrial communications indicates the existence of a number of distinct anatomic and clinical varieties of this condition (Table 1). The anomalies with which we are concerned in this presentation are classified under the general heading of "endocardial cushion defect." Recently, two of us and an associate[1] published the results of an experience with these endocardial cushion defects, in general. This presentation is limited to a review of the concepts concerning the variety of endocardial cushion defects known as "persistent common atrioventricular canal" and brings our experience with this malformation up to date.

Rogers and Edwards[2] suggested the term "persistent common atrioventricular ostium" and, later, Wakai and Edwards[3] employed the term "persistent common atrioventricular canal" and divided the condition into the partial and complete forms. The term "endocardial cushion defect," previously proposed by Watkins and Gross,[4] has been adopted by us as a general heading for these defects and for other related ones. A detailed presentation of our experience with defects of the common atrium type has been published.[5]

Embryology

The term "endocardial cushion defect" seems appropriate when the embryology of this congenital cardiac anomaly is recalled. The embryonic division of the heart into its four chambers involves the growth and final convergence of the atrial septum, the ventricular septum and the endocardial cushions.[3] Defective development of the endocardial cushions, it is believed, is responsible in great part for the persistent common A-V canal. These two masses of tissue are located ventrally and dorsally. They contribute to the development of the mitral and tricuspid valves by fusion in the midline and may play a part in the closure of the atrial and ventricular septums. Thus, it is clear that defective development of these endo-

Table 1

Types of Interatrial Communications

Patent foramen ovale
Atrial septal defect, usual type (ostium secundum type)
Without anomalous pulmonary venous connection
With anomalous pulmonary venous connection of right lung to right atrium
With insufficiency of atrioventricular valves
High atrial septal defect with anomalous pulmonary venous connection of right lung to superior vena cava (sinus venosus type of defect)
Endocardial cushion defect
Partial form of common atrioventricular canal (ostium primum defect with cleft mitral valve)
Complete form of common atrioventricular canal
Common atrium
As an associated defect in the presence of a complicated anomaly such as total anomalous pulmonary venous connection

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cardial cushions can lead to a variety of congenital cardiac anomalies.

Persistent Common A-V Canal

Although transitional stages have been recognized, one can generally divide these defects into two main varieties: the partial and the complete form.

Partial Form: This malformation is entitled by some, "ostium primum defect with mitral cleft." There is no interventricular communication in it. The anterior leaflet of the mitral valve has exhibited a cleft or notch in all cases in this series. There is a defect between the two atria, the lowermost border of which is composed of an atrioventricular valve (Fig. 1). There may be a second defect in the region of the foramen ovale. Usually, the septal leaflet of the tricuspid valve is not cleft. Several cases of the partial form of this condition, in which a definite cleft in the tricuspid valve was present, are included in this series.

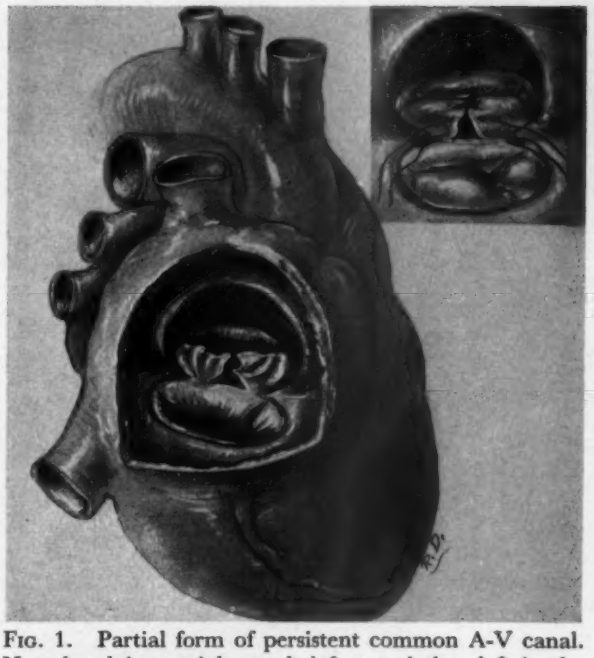


Fig. 1. Partial form of persistent common A-V canal. Note low-lying atrial septal defect and the cleft in the anterior leaflet of the mitral valve. The technic used for repair of the cleft mitral valve is shown in the inset. (Reproduced with permission of the authors and publisher.[1])

Complete Form: In the complete form of the malformation under discussion, both the anterior leaflet of the mitral valve and the septal leaflet of the tricuspid valve have clefts (Fig. 2). These two clefts are continuous, forming a free communication between the free edges of the anterior and posterior leaflets of the common atrioventricular valve (Fig. 2a).

Between the two sides of the heart, there is a defect, which has an atrial and a ventricular

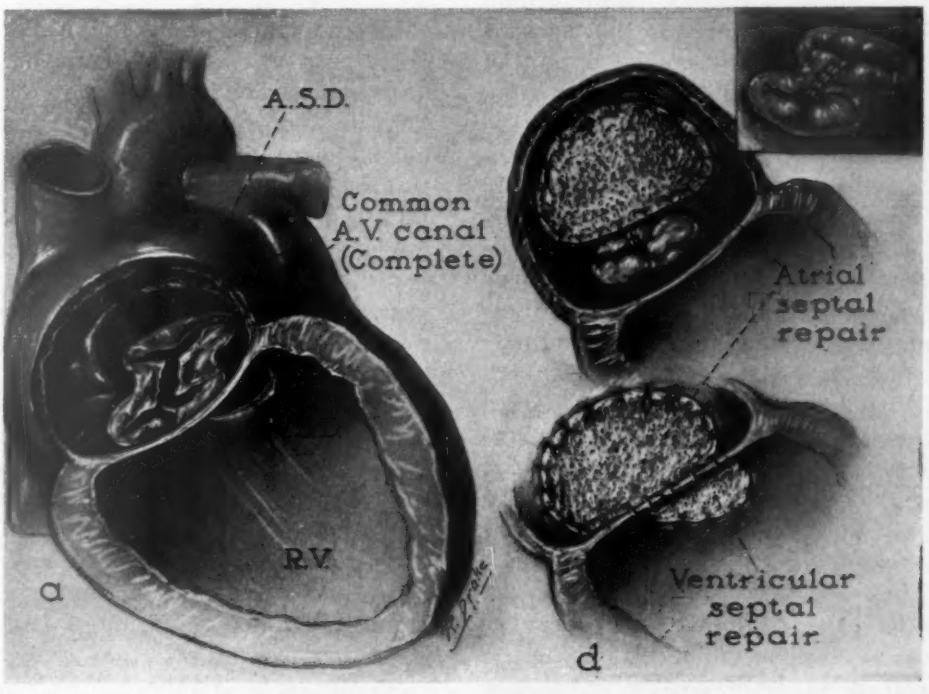


Fig. 2. Complete form of persistent common A-V canal. (a), large interventricular communication (V.S.D.) should be noted. (b), suture of cleft in leaflets of mitral and tricuspid valves. (c), new atrial septum in place. (d), closure of both atrial and ventricular septal defects. (Reproduced with permission of the authors and publisher.[1])

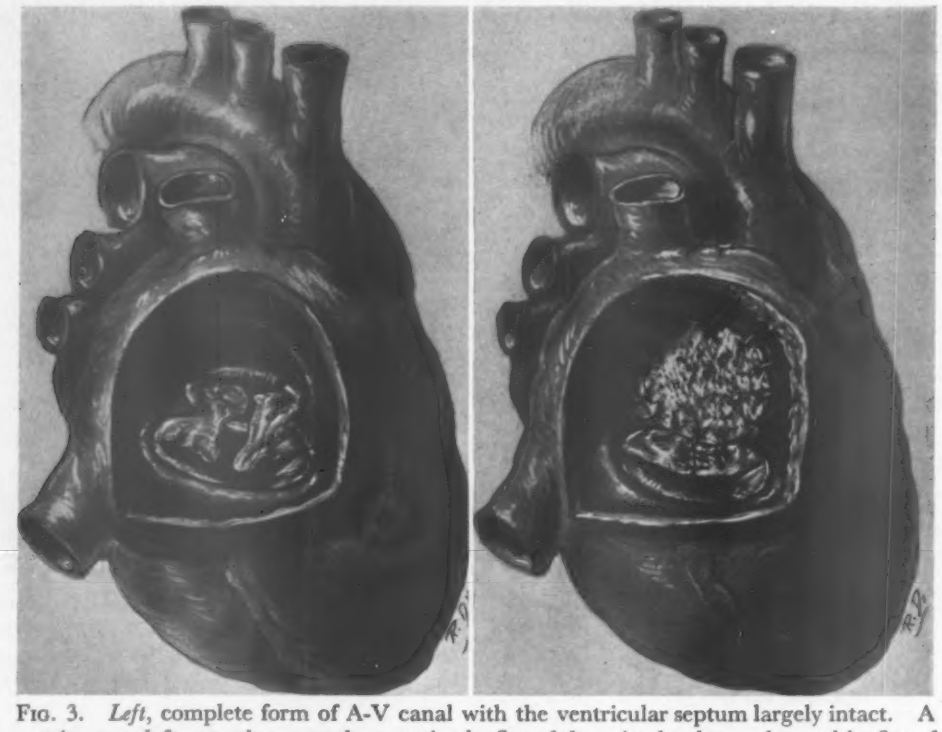


FIG. 3. *Left*, complete form of A-V canal with the ventricular septum largely intact. A continuous cleft extends across the anterior leaflet of the mitral valve and septal leaflet of the tricuspid valve, in addition to the characteristic interatrial communication. *Right*, repair of complete form of A-V canal without a pronounced interventricular communication. (Reproduced with permission of the authors and publisher.[1])

component. The atrial component is similar to that seen in the partial form of the malformation. Although the atrial component of the defect is rather uniform from case to case, the amount of ventricular septum, which forms the lower edge of the defect, varies. Inferior and anterior to the anterior leaflet of the common atrioventricular valve, the ventricular septum usually has a wide concave defect, allowing free interventricular communication. This defect usually extends posteriorly to involve the space under the cleft separating the anterior and posterior leaflets of the common atrioventricular valve. Inferior to the posterior leaflet there may be shortened chordae tendineae attached to the ventricular septum. Between these chordae are spaces allowing further interventricular communication.

Occasionally, the defect in the interventricular septum is not extensive and may consist only of a small defect beneath the continuous cleft in the atrioventricular valve, combined with spaces between shortened chordae tendineae joining the anterior and posterior leaflets to the ventricular septum (Fig. 3).

CLINICAL DATA

As of July 1959, a total of sixty-six patients with persistent common A-V canal have undergone repair at the Mayo Clinic, with extracorporeal circulation being used (Table II). Forty-seven of these patients have been reported on previously by two of us and an associate.[1] Of the sixty-six patients, forty-eight had the partial form; their ages ranged from ten months to forty-nine years and averaged twelve years. Eighteen patients had the complete form of the malformation; their ages ranged from ten months to fifty-one years and averaged eight years. With the exception of one patient in the latter group, all were sixteen years of age or younger.

Sixteen of the patients with the partial form of A-V canal had no symptoms, although each had objective evidence of significant hemodynamic disturbance. Only three had marked symptoms, whereas eleven of the eighteen patients with the complete form had severe symptoms consisting of episodes of frank cardiac failure, attacks of pneumonia or marked exertional limitation.

Significant pulmonary hypertension was found in sixteen of the forty-eight patients with the partial form of the defect, whereas in all but one of the eighteen patients with the complete form

TABLE II
Clinical Data on the Sixty-six Patients Undergoing Operations

Type of Defect	No. of Total Cases	Age (yr.)		Symptoms		Pulmonary Hypertension*		
		Average	Range	Mild or Moderate	Marked or Severe	None or Mild	Moderate	Severe
Partial A-V canal	48	12	10 mo. –49	29	3	32	11	5
Complete A-V canal	18	8	10 mo. –51	7	11	1	4	13

* Pulmonary artery systolic pressure between 40 and 70 mm. Hg indicates moderate pulmonary hypertension and that in excess of 70 mm., severe pulmonary hypertension.

elevation of the pulmonary artery pressures was significant. In thirteen patients with the complete form, the pressure was markedly elevated, being in excess of 70 mm. Hg.*

DIAGNOSIS

In the partial form of A-V canal, the physical findings are similar in many respects to those encountered in patients with atrial septal defects of the usual type. Yet, the presence of a harsh murmur along the lower left sternal border, at the apex, or at the sides, related to insufficiency of one or both of the atrioventricular valves, may differentiate patients with common A-V canal from those with ordinary atrial septal defect.

The diagnostic value of the vectorcardiogram in this group of patients must be stressed. This subject is discussed in detail in another article in this symposium.[6] As pointed out by Toscano-Barboza and his associates,[7] the characteristic finding in patients with persistent common A-V canal is a counterclockwise rotation in the frontal projection, usually above the isoelectric point, of the instantaneous vectors composing the QRS loop. In some instances, the frontal vectorcardiogram shows a characteristic narrow figure-of-eight configuration of the QRS loop.

Occasionally, a similar vectoral loop will be seen in other forms of congenital heart disease. Toscano-Barboza and his associates[7] found seven patients with vectorcardiograms similar to those described among one hundred patients with the ordinary type of atrial septal defect.[8] Nine of fifty-six patients (15 per cent) with ventricular septal defects were found by Toscano-Barboza and DuShane[9] to have QRS vectors similar to the type described as characteristic of persistent common A-V canal. On the other hand, only one of the vectorcardiograms on our patients with persistent common A-V canal was somewhat atypical of this condition.

* Pulmonary artery systolic pressure between 40 and 70 mm. Hg indicates moderate pulmonary hypertension and that in excess of 70 mm., severe pulmonary hypertension.

SURGICAL REPAIR

Open cardiotomy is obviously desirable for the repair of all forms of common A-V canal, and whole body perfusion is at present the best way of supporting the patient during intracardiac repair. All of the patients reported on herein have undergone open heart operations for which total cardiopulmonary bypass was attained by employing a Gibbon-Mayo pump oxygenator. In the majority of cases, a bilateral intercostal incision was used, although in some cases a right anterolateral incision was utilized. The midsternal incision has been used in recent cases and provides excellent exposure.

Partial A-V Canal (Fig. 1): Closure of the cleft in the anterior leaflet of the mitral valve is an essential part of the repair whether or not mitral insufficiency is present. Interrupted sutures of 5-0 silk are used for careful approximation of the cleft leaflet (Fig. 1 inset). This portion of the repair is carried out while the heart is beating to permit evaluation of the effectiveness of the repair. With the heart arrested by anoxia, the interatrial communication is closed with a prosthesis of woven Teflon.® A stitch is placed in the midpoint between the atrioventricular valves. The repair is carried out in a counterclockwise direction, with either continuous or interrupted sutures, until the region of the coronary sinus is reached. Then the heart is started again by releasing the aortic clamp and the remainder of the repair of the interatrial defect is carried out with interrupted silk sutures while

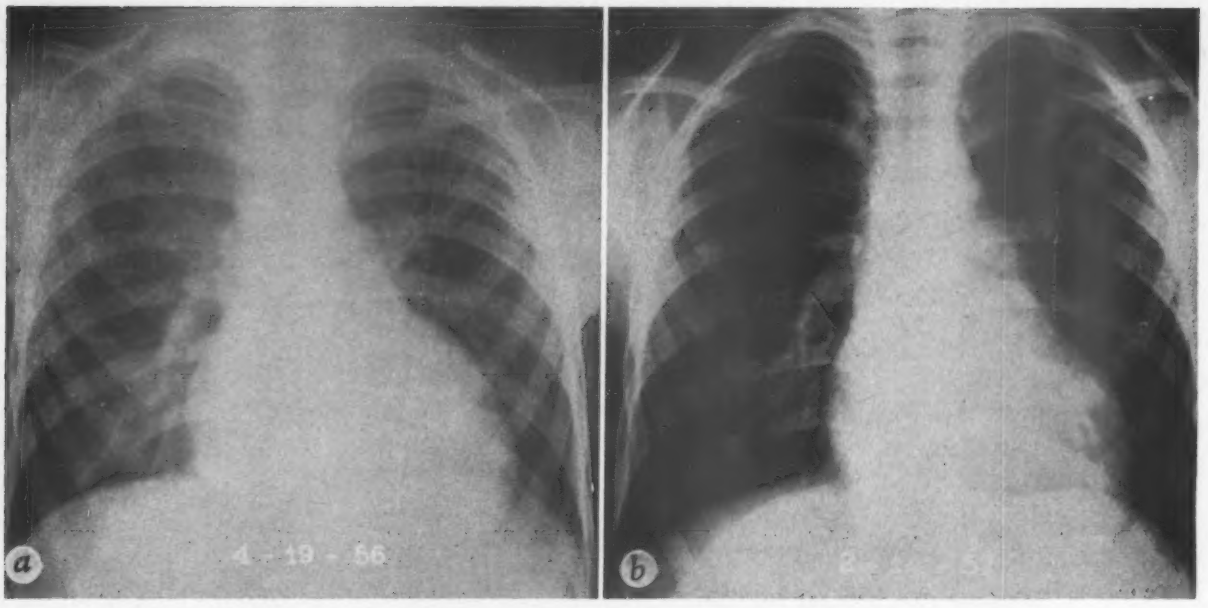


FIG. 4. Thorax of patient with partial form of persistent common A-V canal. (a), before operation. (b), ten months after operation. Note decrease in size of heart and normal pulmonary vascular markings.

the heart is beating. In this way, any interference with the conduction system can be detected and the offending suture removed.

Complete A-V Canal: Repair of the complete form of this anomaly is more difficult than repair of the partial form. The technic is far from standardized. One step involves suturing the anterior and posterior leaflets of the common atrioventricular valves together in the midline to obliterate the communicating cleft. Then the cleft anterior leaflet of the mitral valve and the cleft septal leaflet of the tricuspid valve are repaired with interrupted silk sutures (Fig. 2b). When the interventricular communication is not pronounced, consisting mainly of spaces between shortened chordae tendineae which join the leaflets of the common atrioventricular valve to the underlying septum, the repair may be completed easily from the atrial approach (Fig. 3, left). A prosthesis is sutured in place to obliterate the interatrial communication (Fig. 3, right). The lower margin of the prosthesis is sutured through leaflet tissue to engage the underlying ventricular tissue. Particular care must be taken to avoid injury to the bundle of His.

When a large ventricular septal defect is present, this part of the repair may generally be undertaken as just described, or through an incision in the right ventricle. If the latter method is undertaken, anoxic cardiac arrest is employed, the right ventricle is opened, and the ventricular septal defect is repaired. A semicircular, somewhat teardrop-shaped prosthesis has been employed in some cases, suturing it in place so that its base or straightest edge is attached to the under surface of the atrioventricular valvular tissue. The heart is re-started by releasing the aortic clamp, and the ventricular incision is closed. The remainder of the repair is completed through the incision in the atrium. A second prosthesis is inserted, the inferior edge of which is sutured through leaflet tissue to the underlying ventricular septal prosthesis (Fig. 2c and 2d). It is not certain at present which of the two methods of managing the ventricular portion of the defect is preferable.

RESULTS

Partial A-V Canal: Two hospital deaths occurred among forty-eight patients in this group, a mortality rate of 4.2 per cent (Table III). Two late deaths occurred as a result of a Stokes-Adams attack six weeks and nine months after operation. Besides these two patients with A-V dissociation, two patients have had this complication to date, but it has not caused them any particular difficulty.

The repair has been judged as adequate in all surviving patients, and as complete in thirty-six of the surviving forty-four patients on the basis of operative and postoperative appraisals, which include postoperative thoracic roentgenograms in many cases (Fig. 4) and, in some instances, postoperative cardiac catheterization (Fig. 5). The majority of patients had a soft pulmonic systolic

TABLE III
HOSPITAL MORTALITY FOLLOWING REPAIR

Type of Defect	No. of Total Cases	Hospital Deaths	
		No.	Per cent
Partial A-V canal	48	2	4.2
Complete A-V canal	18	12	66.7
Total	66	14	21.2

murmur along the left sternal border after operation. Twelve patients had a persistent, soft, apical systolic murmur, suggestive of some residual mitral insufficiency; but none has had clinical symptoms of cardiac disability. One of these patients underwent cardiac catheterization after operation and, in addition to slight mitral insufficiency, was found to have a residual left-to-right shunt of 15 per cent.

Complete A-V Canal: In contrast to the excellent results of operation in the preceding group, surgical repair of the complete form of the defect was accompanied by a disappointingly high mortality rate. Of the eighteen patients in this group, twelve died during the postoperative period, a hospital mortality rate of 66.7 per cent. An additional patient died at home two months after operation, following a fulminant illness of a few hours' duration during a local epidemic of influenza. At necropsy, the repair was found to be intact and complete.

A variety of factors seemed to be responsible for the failure of so many of these patients to survive, the chief ones being heart block, persistent incompetence of the atrioventricular valves, progressive myocardial failure with low cardiac output and irreducible pulmonary hypertension. Of the six survivors, only one had a large interventricular communication. The remaining five had defects of the transitional variety with small openings between the shortened chordae that join the atrioventricular valves to the ventricular septum. None of these five patients required an incision in the ventricle, since all the repair was able to be accomplished from the atrial side. Another anatomic feature of considerable importance in this group of patients was the status of the mitral valve. Complex derangements of this valve were common among those who failed to survive, and complete repair was not always possible. Despite these disappointments with the complete

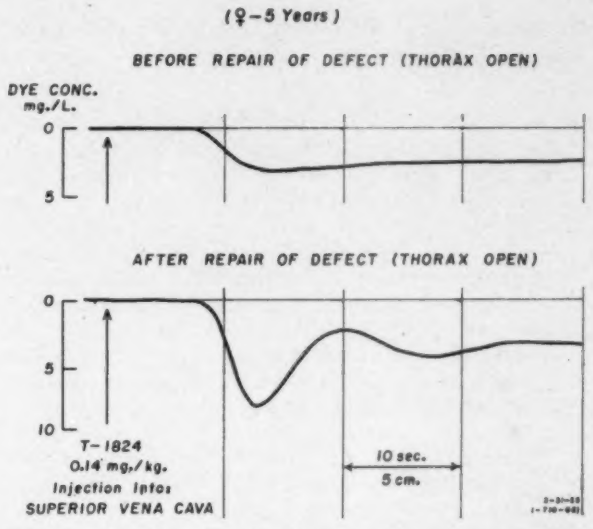


FIG. 5. Arterial dye dilution curves recorded before and after surgery for repair of partial form of persistent common A-V canal. The arrow indicates the instant of injection of the dye. *Upper panel*, preoperative dye curve. Note the shallow deflection and the prolongation of the disappearance slope indicative of large left-to-right shunt. *Lower panel*, postoperative dye curve. Its configuration is normal.

form of common A-V canal, progress is being made in understanding the surgical problems presented by this lesion. This should be reflected in some lowering of hospital mortality rate.

SUMMARY

Persistent common A-V canal is only one of a wide variety of interatrial communications. This condition includes defects of one or both septums and one or both atrioventricular valves. The over-all term of "endocardial cushion defect" has been used to designate these and other similar congenital heart defects.

Our surgical experience includes forty-eight patients with the partial form of the defect and eighteen with the complete form. Extracorporeal circulation was used for all operations. There were two hospital deaths among patients undergoing repairs of the partial form, a mortality rate of 4.2 per cent, whereas twelve of the eighteen patients with the complete form died, a mortality rate of 66.7 per cent.

ADDENDUM

From July, 1959 to July, 1960, twenty additional patients with persistent common atrioventricular canal have undergone operation. Eighteen had the partial form and two the complete form of the defect. One patient with

the partial form died after operation, as did one with the complete form.

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Results of Surgical Treatment of Atrial Septal Defects

Particular Consideration of Low Defects Including Ostium Primum and Atrioventricular Canal*

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DEFECTS of the atrial septum are common congenital cardiac anomalies which vary widely in anatomic characteristics and in the degree of cardiac dysfunction produced. The nature of the anomaly depends upon developmental defects that appear during the fourth to sixth week of embryonic life. Thus, defects located high in the septum above the annular attachments of the A-V valves result from failure of the septum secundum to fulfill a role in forming the atrial septum and closing the foramen ovale. Defects located low in the septum are produced by improper development of the septum primum.

The septum primum is responsible for the closure of the ostium primum which lies just above the ventricular septum and endocardial cushions. In most instances when the ostium primum remains open, the endocardial cushions are also incompletely formed, producing clefts or even large gaps in the septal leaflets of the mitral and tricuspid valves. Frank failure of the endocardial cushions to converge centrally in the closure of the A-V canal results in a persistent or common A-V canal or atrioventricularis communis. In this complicated anomaly the leaflets of the mitral and tricuspid valves are not securely attached to the upper margin of the ventricular septum, but are suspended in a floating position by chordae tendineae. Under these circumstances, and because of the insufficient amount of valve tissue present, a common anterior and posterior leaflet is formed and incompetent mitral and tricuspid valves result.

CLASSIFICATION OF DEFECTS

Since classification of these lesions is not standardized, each report of this type must include definitions of the terminology used. For the purposes of this report, therefore, three main categories of atrial septal defect will be considered in analyzing our experience: (1) *The high or septum secundum defects* are those involving the upper septum, which is formed by the embryonic septum secundum, and include foramen ovale defects, inferior caval defects, superior marginal or sinus venosus defects and various associated partial anomalies of the pulmonary venous drainage (Fig. 1). (2) *Ostium primum defects* involve the lower portion of the atrial septum in close relation to the ventricular septum, with no margin of tissue above the annulus of the A-V valves (Fig. 2). In these cases a cleft is usually present in the mitral valve, producing mitral regurgitation and left ventricular hypertrophy.[1] An important finding in this area was the observation that the annulus of the mitral valve was normally attached to the superior rim of the interventricular septum. (3) *Common A-V canal* includes all of the low defects in which the leaflets of the mitral and tricuspid valves are cleft with common leaflets, anteriorly and posteriorly, and in which the leaflets are suspended above the superior margin of the ventricular septum (Fig. 3). Thus, in these defects openings were present between the left and right sides of the heart both in the atria and ventricles (Fig. 3). Frequently, the deformity was extreme and associated with a large inter-

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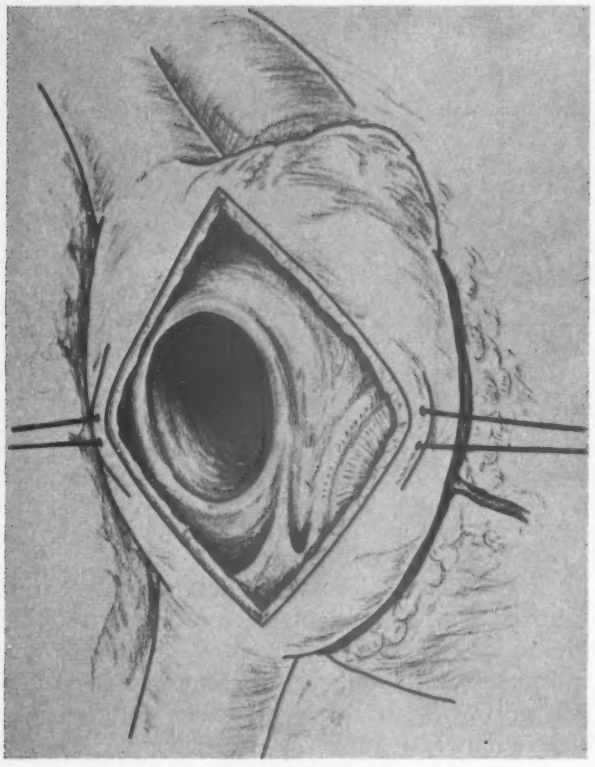


FIG. 1. Drawing showing the most common type of septum secundum interatrial defect. Also included in this category of defects are the sinus venosus lesion, inferior caval defects and partial anomalous pulmonary venous drainage.

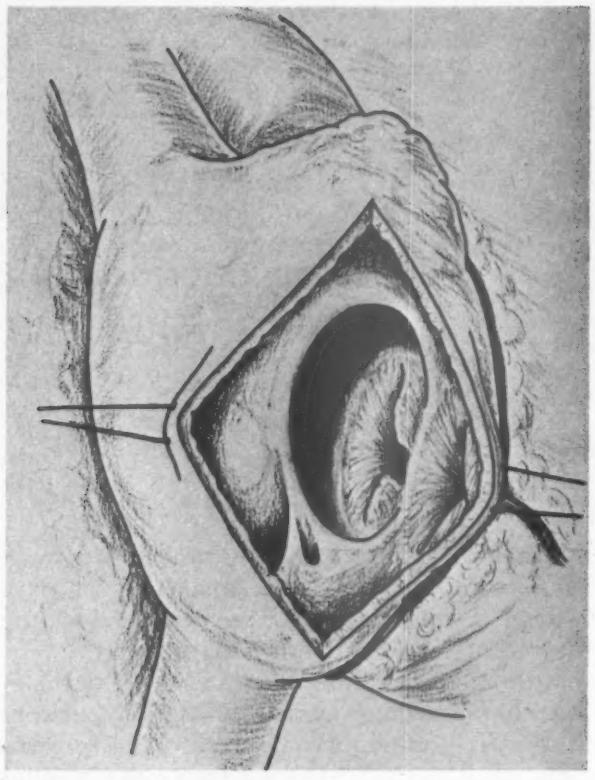


FIG. 2. Drawing showing typical ostium primum type of atrial septal defect located low in the septum close to the mitral and tricuspid valves. A cleft mitral valve which produces mitral regurgitation and contributes to a large left-to-right shunt is demonstrated.

ventricular communication. In very young patients, poorly developed mitral and tricuspid valves were demonstrated and the heart functioned predominantly as a single-chambered organ.

SURGICAL TECHNICS

Although we previously used several technics for surgical correction of the high or ostium secundum type of atrial septal defect, the best results in all atrial septal lesions have been obtained with the pump oxygenator, used for temporary cardiopulmonary bypass. Since April 9, 1956, when our first patient with atrial septal defect was operated upon using the pump oxygenator, this method has been used exclusively for the repair of atrial defects of all types.[2]

Indeed, atrial defects have constituted one of the major groups of congenital lesions for which open heart surgery was performed (Table 1). A bubble diffusion oxygenator was used in all open heart operations.[3] Venous blood was removed from the venae cavae by pump siphon and delivered to the oxygenator. Oxygenated blood was returned to the femoral artery. Induced cardiac arrest with dilute potassium citrate solution was used in a few early cases, but this proved to be unnecessary and associated with certain complications.

Since that time a technic of intermittent occlusion of the ascending aorta has been used to reduce coronary venous return. This method has several advantages, but of particular importance is the fact that it permits prompt recognition of conduction disturbances during the period of septal repair. Simplicity of operation of the pump oxygenator has been achieved and blood requirements have been reduced to 4 to 6 pints for each operation. Complications secondary to the pumping apparatus and oxygenator alone are rare. Usually, complications can be attributed entirely to the complicated nature of the anomaly for which the operation is being performed.

RESULTS

Septum Secundum Defects: During the past three and a half years, a total of 191 patients with atrial septal defect were operated upon using

TABLE I

Lesions for Which Temporary Total Cardiopulmonary Bypass Was Used (Before June 1959)

Lesion	No.	
Congenital		
Ventricular septal defect	218	
Atrial septal defect	191	
septum secundum	138	
ostium primum	29	
A-V communis	24	
Tetralogy of Fallot	52	
Aortic and subaortic stenosis	30	
Pulmonic and infundibular stenosis	32	
Total anomalous pulmonary venous drainage	16	
Sinus of Valsalva fistula	4	
Transposition of great vessels	6	
Aorticopulmonary septal defect	2	
Miscellaneous lesions	16	
Subtotal		567
Acquired		
Calcific aortic stenosis	40	
Aneurysm of ascending aorta	15	
Mitral stenosis	11	
Mitral insufficiency	10	
Aortic insufficiency	5	
Myocardial infarction	11	
aneurysm of left ventricle	9	
ventricular septal defect	2	
Myxoma	4	
left atrium	3	
right atrium	1	
Traumatic	3	
aortic ventricular fistula	2	
ruptured papillary muscle	1	
Subtotal		99
Total		666

TABLE II

Results of Surgical Treatment of Atrial Septal Defects

Defect	No. of Cases	Deaths	Mortality (%)
Septum secundum*	138	8	5.8
Ostium primum†	29	4	13.0
A-V canal (complete)	24	16	64.0
	191		

* Twenty-eight patients over twenty-five years of age—28% mortality. One hundred ten patients under twenty-five years of age—0% mortality.

† Twenty-two patients with mitral cleft—18% mortality. Seven patients without mitral cleft—0% mortality.

cardiopulmonary bypass[2] (Table II). Among these patients, the most common lesion was the septum secundum defect. All defects located high in the septum were closed with silk sutures, either interrupted or continuous. Sinus venosus defects were usually repaired with a small patch of Dacron® cloth to prevent distortion and constriction of the ostium of the superior vena cava. Complete A-V dissociation did not occur after operation in a single patient. Several factors were important in determining operative risk in patients with septum secundum lesions. It was of interest that in 110 patients under twenty-five years of age no postoperative deaths occurred, despite the fact that, in several, pulmonary hypertension was present and systolic pressures exceeded 60 mm. Hg. On the other hand, patients over twenty-five years of age presented a more serious problem from the standpoint of surgical risk, since eight of twenty-eight died following surgery. Nine patients with septum secundum defects were over forty years of age, and four of these died following operation. Three patients were over fifty years of age, and two died; but both had almost intractable failure prior to operation.

The results of operation in patients of ad-

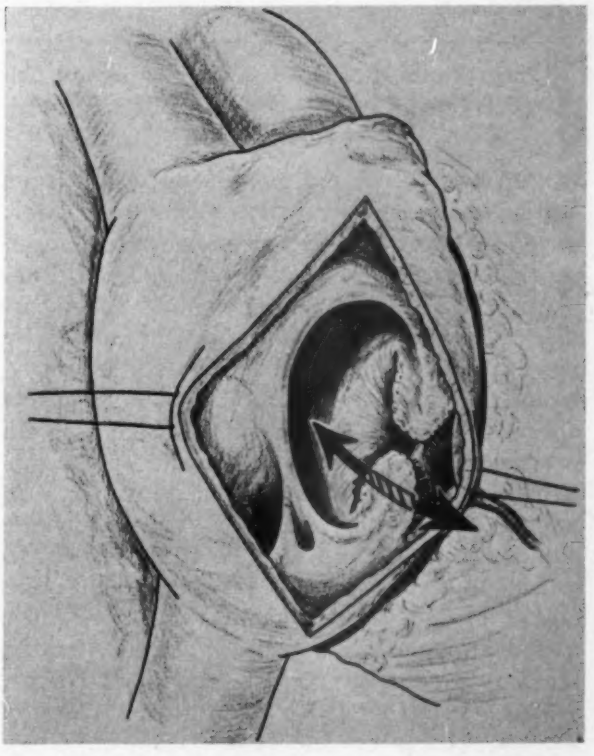


FIG. 3. Drawing showing a common persistent A-V canal. The septal defect in this lesion involves both the atrial and ventricular septums. Mitral and tricuspid valvular anomalies are often severe, with the common valve leaflets suspended above the ventricular septal defect.

TABLE III
Results of Operation in Nine Patients* With Atrial Septal Defect (Septum Secundum) and Pulmonary Hypertension

Case No.	Age (yr.)	Sex	Pulmonary Pressure (mm. Hg)	Date of Operation	Result
1	42	F	90/25	6/2/56	Recovered
2	50	F	70/36	6/27/56	Died, 72 hrs. after surgery
3	39	F	110/40	7/6/56	Recovered
4	27	M	75/30	8/10/57	Died, 72 hrs. after surgery
5	55	M	80/40	11/11/57	Died, 17 days after surgery
6	38	F	100/45	3/12/58	Died, 72 hrs. after surgery
7	48	M	70/40	11/20/58	Died, 36 hrs. after surgery
8	25	F	70/25	2/23/59	Recovered
9	32	F	70/30	5/11/59	Died, 48 hrs. after surgery

* Patients over twenty-five years of age with pulmonary pressure more than 60 mm. Hg systolic.

vanced age with severe pulmonary hypertension and septum secundum defects are shown in Table III. This group of nine patients, with three survivors following operation, does not reflect the entire problem with these patients. Although cardiac catheterization has not been performed on any of the survivors, clinically they still have pulmonary hypertension. As a consequence of operative closure of the defect, each has experienced subjective improvement. Most patients with pulmonary hypertension seem to tolerate operation well, and the immediate clinical course appears to be satisfactory. In some, however, acute severe cardiac failure ensues forty-eight to seventy-two hours later, and death may occur rapidly despite vigorous medical attempts to control pulmonary edema.

Our experience with complicated cases of septum secundum defects is similar to others that have been reported. McGoon and his associates[4] describe five factors that adversely affect operative mortality in septum secundum defects; namely, the presence or history of congestive heart failure, a right-to-left intracardiac shunt of 10 per cent or more, increased right atrial pressure, pulmonary arterial pressure exceeding 75 mm. Hg and a ratio of pulmonary resistance to peripheral resistance of 0.5 or more. Although these authors do not believe that age is a factor in prognosis following operation, our results strongly suggest that young patients tolerate operation better than older ones, even though pulmonary hypertension may be present. Our policy is to recommend surgical repair of septum secundum atrial defects in all patients under fifteen or twenty years of age with significant left-to-right shunts regardless of the degree of pulmonary hypertension. Selection of older patients, i.e., those over twenty-five years of age, should be made more cautiously with careful consideration of the adverse factors already mentioned. Risk in the older patient with high pulmonary vascular resistance may be prohibitive and, even if operation is tolerated, the ultimate result may be disappointing. The use of perforated patches sutured into the defect to permit gradual interruption of the shunt has been disappointing in our cases.

Ostium Primum Defects: Twenty-nine patients with this defect, ranging in age from four to forty-five years[5] (Table II), were operated upon. Repair of the cleft in the mitral valve was accomplished with interrupted silk sutures; in no instance did the valvuloplasty disrupt following operation. The valvuloplasty was performed on that portion of the valve located close to the annular attachment. Placement of sutures along the lower margin of the valve was avoided, since impairment of valve function and partial mitral stenosis could be produced in this manner. Repair of the interatrial communication was usually made with a prosthesis of Dacron or compressed Ivalon.® Avoidance of traction on the repair may be important both to insure stability of the closure and to avoid injury to the conduction fibers. Sutures along the inferior margin of the defect, particularly those near the center and between the center and the ostium or the coronary sinus located posteriorly, were placed very carefully. These sutures were tied individually with the heart beating actively to detect any disturbance attributable to an individual suture. Replacement of an offending suture could then be accomplished, avoiding a difficult conduction complication after operation.

Third degree heart block or complete A-V dissociation occurred in eight patients after operation. One of these patients died, three

converted to sinus rhythm spontaneously, and in four the block was still present four weeks or more after operation. Our experience with the electrical pacemaker has not been favorable in these or other patients after open heart surgery, but in general we have used the pacemaker only in the more desperate cases. Isoproterenol, administered intravenously and sublingually, has produced the best results in patients with complications arising from injury to the conduction system. Isoproterenol therapy was continued as long as the patient was having a reduced cardiac output resulting from the bradycardia.

All four patients who died after operation had more than usual manifestations of cardiac impairment, since the mitral regurgitation and pulmonary hypertension were greater than in the average cases. Extreme enlargement of the left ventricle may therefore be considered an unfavorable prognostic sign. The presence of a right-to-left shunt of more than 10 per cent is also a serious prognostic finding. It may be concluded, however, that repair of ostium primum defects of the atrial septum can be accomplished with an acceptable risk (13 per cent in our series) and surgical treatment is advisable in the majority of cases.

A-V Canal (Complete): Technic of surgical repair of this type of defect was not standard in our cases, since the lesion itself was so variable.[5] Usually, the lesion was exposed through an atriotomy incision. The floating valve leaflets were attached to the superior margin of the ventricular septum with interrupted through-and-through sutures. Clefts in the A-V valves were repaired by sutures and the clefts were closed. After this preliminary reconstruction of the canal the residual interatrial communication was closed with a generous patch of Dacron cloth, using the same precautions as in repair of ostium primum defects. In the most complicated defects a variety of additional technics were attempted, including right ventriculotomy, to repair the subvalvular portion of the lesion. In some of the lesions, particularly in infants with cardiac failure, the defects could not be completely corrected with restoration of normal valvular function. This undoubtedly accounted for the high morbidity and mortality in these patients.[6]

Results of operation in these patients have been disappointing in the entire series. Early mortality after operation was 64 per cent in twenty-four cases (Table II). Eight patients were under twenty months of age, however, and had manifestations of almost intractable heart failure; seven died after operation. On the other hand, of sixteen patients over two years of age, nine died, representing somewhat more favorable results. The oldest patient in the series, who was aged sixteen years and had pulmonary hypertension associated with a right-to-left shunt, died four days later from complete heart block and right-sided failure. Injuries to the conduction system are even more common in this lesion than in the ordinary ostium primum defect, since the A-V bundle is in a more vulnerable position. When conduction disturbances occurred, the survival was low because of other problems such as residual valvular incompetence. Although the results in this series of cases were disappointing in general, results in the eight survivors were moderately encouraging, several patients having been completely restored to a normal life.

This experience suggests that further improvement in statistics will follow more careful selection of patients. If critically ill infants, patients with right-to-left shunts and those with cardiac decompensation were to be eliminated, the good results of operation would increase. However, the need for relief of symptoms in these patients often exceeds consideration of conservative judgment, and operations are still performed despite great risk.

Summary

Repair of defects in the interatrial septum was performed in 191 patients, using the pump oxygenator for temporary cardiopulmonary bypass. Results of operation were related to the nature of the defect and the extent of the cardiac impairment. In uncomplicated cases of septum secundum defects, the risk of surgery was nil and results of closure excellent. In a consecutive series of 110 patients under twenty-five years of age, no deaths occurred. Repair of ostium primum defects with cleft mitral valve was performed in twenty-nine patients, with a 13 per cent mortality. Long-term results were highly favorable and indicate complete repair of this defect. Results in surgical treatment of a complete A-V canal were the least favorable. Congestive heart failure, pulmonary hypertension, right-to-left intracardiac shunts, extremes of age and the nature of the anomaly determine risk of operation.

Addendum

Since this paper was submitted, the total series of patients undergoing temporary cardiopulmonary bypass has increased to 970. Among these patients, 268 had atrial septal defects and 206 had septum secundum type, thirty-five had ostium primum and twenty-seven had common A-V canal. The surgical mortality in ostium primum type of atrial septal defect has been 11 per cent in the entire series of thirty-five patients.

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The Surgical Repair of Persistent Atrioventricular Canal

Results in Twenty-Six Operative Cases*

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THE A-V canal is an infrequent lesion in the statistics of open heart surgery. At the beginning of 1959, Lillehei and Thevenet[1] reported thirty-two cases of A-V canal in 404 heart operations (6 per cent). In 1958, Cooley et al.[2] reported eight cases in 162 operations (6 per cent); and Kirklin and his associates[3] reported eighteen operative cases in 145 patients (7.4 per cent).

As of June 1959 our own statistics showed that an A-V canal was present in twenty-six of the 172 patients we operated upon using extracorporeal circulation (15 per cent). With one exception (our first operation using extracorporeal circulation in 1955), all these operations took place during the last two years (1957 to 1959). Ten patients were males and sixteen females; their ages ranged from six to thirty-nine years, with seventeen children from six to twelve, three adolescents from fourteen to seventeen and sixteen adults from twenty-one to thirty-nine years of age.

The analysis of our twenty-six cases (Table 1) enables us to make the following observations on the anatomic characteristics of the malformation, its surgical cure and the results obtained.

ANATOMIC CHARACTERISTICS OF THE LESION

In grouping the ostium primum defects with A-V canal in this study, we have adhered to the custom of making no nosological distinction and merely discussing the A-V canal as opposed to the atrial septal defect of the ostium secundum type. Several factors favor this grouping: the probability of a close embryologic origin, clinical and electrocardiographic features so similar that surgical exploration alone allows a precise diagnosis and, most important, the fact that both the ostium primum defect and A-V canal need to be repaired using extracorporeal circulation, contrary to what is required in the repair of atrial defects of the ostium secundum type.

Our series included two patients with an ostium primum defect and no valvular lesion (Cases 23 and 24) and two with single auricles, one without a valvular lesion (Case 25) and the other with a cleft mitral valve (Case 9).

These particular lesions make the grouping of all malformations whose common characteristic is a defect of the atrial septum reaching down to the ventricular septum even more important.

Among the different forms of A-V canal encountered, it is already classic to differentiate between the partial and total forms. The partial form is represented by an ostium primum defect accompanied by a cleft mitral valve. The complete form consists of an ostium primum defect complicated by a defect of the interventricular membranous septum and a grave alteration of both mitral and tricuspid valves. In reality, our surgical and anatomic findings have shown that the lesions do not always conform strictly to pattern, and a whole series of intermediate stages exists between the ostium primum defect and the large A-V canal defect.

In the most favorable cases, the mitral valve is merely cleft without any loss of substance. Very often, more serious alterations are present; for example, a cleft large enough to constitute an actual loss of substance, or a retraction, or an heterogenous aspect, which sometimes goes as far as to have a cribriform structure, or anomalies of the thinness and length of the suspension system. The septal cusp of the tri-

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TABLE I

Anatomical Characteristics, Surgical Procedure and Results in Twenty-Six Cases of A-V Canal

Type of Defect	Case No.	Age (yr.)	Date	Extracorporeal Perfusion		Septal Valvular Lesions		Surgical Repair		A-V Block	Postoperative Course
				Flow (cc./min.)	Time (min.)	Mitral	Tricuspid	Septal Defect	No. of Mitral Sutures		
Partial A-V Canal	1	9	1/57	1,500	34	Cleft	Normal	Ivalon Patch	3	−	Uneventful
	2	6	3/57	1,000	27	Cleft	Normal	Ivalon Patch	4	−	Uneventful
	3	8	1/58	1,300	34	Cleft	Normal	Ivalon Patch	None	−	Death during the operation due to technical mistake: massive pulmonary edema
	4	39	5/58	2,500	30	Cleft	Normal	Ivalon Patch	5	+	Uneventful—persistent A-V block
	5	9	1/58	1,600	?	Cleft	Normal	Ivalon Patch	2	−	Death on third day: pulmonary edema (created mitral stenosis)
	6	9	9/58	1,600	25	Cleft	Normal	Ivalon Patch	1	−	Uneventful
	7	14	1/59	2,800	28	Cleft	Normal	Ivalon Patch	1	+	Uneventful—transitory A-V block
	8	12	4/59	1,800	?	Cleft	Normal	Ivalon Patch	1	−	Uneventful
	9	28	5/59	3,000	45	Cleft	Normal	Ivalon Patch	2	−	Uneventful
Intermediate A-V Canal	10	8	4/58	1,300	23	Cleft	Cleft	Ivalon Patch	2	−	Uneventful
	11	8	11/58	1,500	22	Cleft	Fenestrated	Ivalon Patch	1	−	Uneventful
	12	7	2/59	?	29	Cleft	Fenestrated	Ivalon Patch	1	−	Uneventful
	13	7	4/59	?	25	Cleft + fenestrated large valve	Fenestrated	Ivalon Patch	1	−	Uneventful
	14	12	5/59	2,500	45	Cleft	Atretic	Ivalon Patch	3	−	Uneventful
	15	12	6/59	2,200	45	Cleft	Absent	Ivalon Patch	3	−	Uneventful
	16	5	6/59	1,500	40	Cleft	Atretic	Ivalon Patch	1	+	Death on third day—massive pulmonary edema
Total A-V Cana	17	7	12/55	580	16	Incomplete	Absent	Suture	None	−	Death on second day—hemolysis
	18	17	11/57	3,000	26	Incomplete	Absent	Ivalon Patch	2	−	Death on second day—anoxia with decerebration
	19	9	12/58	1,600	40	Cleft with alteration	Absent	Ivalon Patch	5	−	Uneventful
	20	10	1/59	1,600	40	Cleft with alteration	Absent	Ivalon Patch	4	−	Uneventful
	21	12	4/59	1,800	?	Cleft	Absent	Ivalon Patch	1	−	Uneventful
	22	21	4/59	3,200	39	Cleft	Absent	Ivalon Patch	2	−	Uneventful
Ostium Primum	23	32	1/58	2,800	28	Normal	Normal	Ivalon Patch	—	−	Uneventful
	24	23	1/58	3,500	18	Normal	Normal	Perforated Patch	—	−	Uneventful
Single Auricle	25	14	7/58	2,500	40	Normal	Normal	Perforated Patch	—	+	Death on sixth day—A-V block
Ostium secundum and cleft of mitral valve	26	7	3/58	1,400	24	Cleft	Normal	Ivalon Patch	2	−	Uneventful

cuspid valve which, as a rule, is not affected in the partial form, is often abnormal, due either to retraction of the valvular tissue and its suspension system or to the fact that the valve is reduced to a fenestrated tissue without precise shape. In the total form, the septal cusp is often missing.

All these anatomic variations, added to the difficulty of a precise operative analysis (depth of the operative field, heart movements and frequently inadequate drainage), make a precise classification of the lesions a particularly arduous task.

Figure 1, although still too schematic, shows the anatomic classification of our operative cases. The unusual association of a cleft mitral valve with a large atrial defect of the ostium secundum type was present in one case. We included it in the A-V canal group, this slight nosological deviation being in the interest of the diagnostic problems raised.

We conclude that the embryogenic defect



FIG. 1. Schematic representation of lesions encountered in twenty-six operative cases. A, ostium primum, normal valves (two patients). B, single auricle, one with normal valves, one with mitral cleft (two patients). C, partial A-V canal (eight patients). D, intermediate form, fenestrated tricuspid (four patients). E, intermediate form, absent septal tricuspid (three patients). F, total A-V canal (six patients). G, ostium secundum + mitral cleft (one patient).

resulting in the formation of an A-V canal is also liable to result in a modification of the respective calibers of the mitral and tricuspid annuli. This modification, when present, almost always consists of a reduction of the caliber of the mitral orifice. Before proceeding with corrective surgery, the surgeon can and should carefully determine the mitral caliber by introducing the forefinger into the valvular orifice, through the ostium primum. It is most important to detect the existence of any degree of mitral atresia, otherwise the surgeon runs the risk of provoking a dangerous stenosis during the mitral repair. This therapeutic problem will be discussed later. At this time, we can say that in five of our operative cases the mitral annulus allowed the introduction of the forefinger only.

SURGICAL TECHNIC

The A-V canal and the ostium primum defect are undoubtedly the best indications for performing open heart surgery. The spontaneous prognosis of the defect is always grave. The process of evolution is characteristic: for months or even years, the patient will live comfortably with his defect; suddenly, at an age which varies according to the gravity of the lesion, the heart fails and from then on deteriorates rapidly and relentlessly. It is imperative that the lesions should be diagnosed and the patient operated upon before the stage of heart failure is reached, since this stage also coincides with an important cardiomegaly and an irreversible major pulmonary hypertension (Fig. 2). While it is logicai to wait a few years when dealing with an infant or a very young child who presents no functional impairment and no pulmonary hypertension, in all other cases it is imperative to operate as soon as the diagnosis is made and the hemodynamic exploration completed.

The precision required to make the repair of heart lesions effective and safe prohibits the blind undertaking of such an operation, or its being performed during the too limited time afforded by cardiac drainage under hypothermia. The A-V canal and ostium primum defect are among the less contested indications for extracorporeal circulation. Of the twenty-six patients we operated upon, six were perfused with an artificial heart-lung, using the Melrose disc oxygenator; the others were perfused with the Lillehei-Dewall apparatus.[4] The total duration of the operation varied from sixteen to forty minutes.

Exposure of Heart: In our method of approach, we have gone from one extreme to the other. The bilateral transverse thoracotomy with horizontal sternotomy used in eight of our cases gave a large exposure of the entire cardiac mass, which is convenient for surgical repair and eventual cardiac resuscitation. However, we had to abandon this technic because of the postoperative respiratory consequences resulting from the opening of both pleurae, the operative collapse of both lungs and the serious diminution of the ventilatory amplitude during the immediate postoperative course. Right thoracotomy with resection of the fifth rib was then used in six cases. This procedure guarantees much safer postoperative conditions. However, it gives a poor view of the atrioventricular region and eliminates the possibility of cardiac resuscitation. For this reason, we resorted to a compromise in our last twelve cases that seems to offer the best solution: a right intercostal thoracotomy in the fourth space is extended by a horizontal sternotomy without opening either the left intercostal space or the left pleura. This procedure permits a sufficient exposure of the heart without any untoward effect on respiration.

A full view and inventory of the lesions are of primary importance. We have seen that the preoperative diagnosis may be more or less incomplete and that direct vision alone can give information about the size of the ostium primum and even more about the valvular lesions. The latter are not always easy to detect because they are deeply seated and more complex than the didactic schemas indicate. Also, this deep area is often flooded by coronary blood, the bronchial reflux and the transigmoidal reflux from

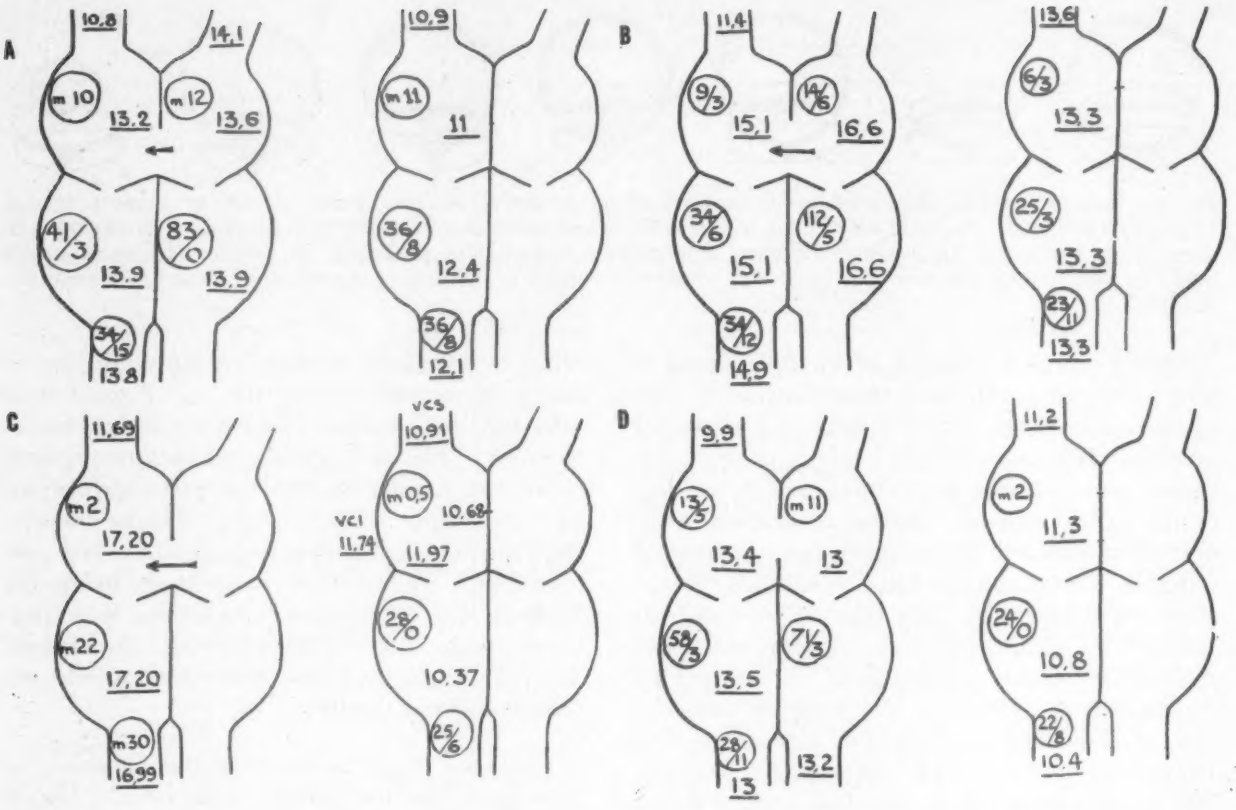


FIG. 2. Hemodynamic results in four operative cases. A, Case 1, partial A-V canal, preoperative (left), one year after operation (right). B, Case 2, partial A-V canal, preoperative (left), six months after operation (right). C, Case 23, ostium primum, preoperative (left), one year after operation (right). D, Case 26, ostium secundum + mitral cleft, preoperative (left), six months after operation (right).

the aortic perfusion at the time of the intracardiac manipulations.

A good aspirator will usually permit adequate drainage. However, should it prove unsatisfactory, discontinuous aortic clamping should be used without hesitation. On one occasion we had to apply the aortic clamp for twenty-seven minutes; this resulted in progressive cardiac arrest by anoxia. At the present stage of our studies, however, we would use potassium citrate to induce heart arrest. We emphasize these facts because we believe that a full view of the lesions is essential to insure a precise and effective repair.

Repair of Valve Defects: The valvular lesions should be repaired first. In five cases we were unable to make a satisfactory repair of the tricuspid valve because of either a cribriform structure of the valvular tissue or the absence of a septal cusp. In only one case (Case 9) was it possible to put a stitch on what seemed to be a cleft in the septal cusp. Fortunately, in such cases, the tricuspid deficiency is probably without serious hemodynamic consequences. At any rate, no such clinical signs were observed in any of the patients operated upon by us. More important and more frequently necessary is the repair of the mitral valve lesion. First, the size of the mitral ring must be determined by inserting the forefinger because, as already stated, the mitral ring is sometimes atretic, and too heavy a valvular stitch may create a mitral obstruction which would be badly tolerated by the patient. In one of our first cases, this technical error resulted in pulmonary edema and death. All repairs should be followed by finger-exploration control. The repair itself, in all cases in which it has been necessary, was effected by means of interrupted sutures on the cleft mitral valve. The number of juxtaposed stitches necessary has varied from one to five, according to the size of the mitral ring.

When this transverse suture ensures perfect closing of a narrow cleft in the middle of a substantial valve, the immediate anatomic result is good, as is the case in the most benign forms of partial A-V canal. Very often, however, the valvular malformation is much more complex, amounting to an actual loss of substance of the larger valve. Approximation of the two valvular stumps, which can be made when the heart is excluded, does not provide a valve of normal consistency, and mitral insufficiency will persist.

This is undoubtedly the most delicate technical and tactical point of the operation. Some authors favor a valvulplasty, using an Ivalon® prosthesis. In the absence of a satisfactory plastic technic, we prefer the

approximate repair by means of sutures, which reduce the mitral deficiency considerably without postoperative risk.

Closure of Ostium Primum Defects: Once the valvular lesions have been repaired, the surgeon proceeds with the closing of the ostium primum defect. The usually large dimension of the latter and the necessity of providing a precise fastening without any traction at the upper extremity of the interventricular wall, has led us to prefer a semicircular patch cut from a sheet of pressed Ivalon. At the time of our first operation in 1955, we used interrupted sutures which did not prove very satisfactory. Since then, we have always resorted to the Ivalon prosthesis. The Ivalon patch must first be set in proper position and then sutured, first at the upper extremity of the interventricular wall and then on to the anterior, upper and posterior border of the ostium primum by a series of interrupted sutures. This method of securing the Ivalon patch, which in our cases has required from ten to twelve stitches, is not really difficult, but requires meticulousness. The only dangerous point lies at the junction of the lower border (the upper extremity of the interventricular wall) and the posterior border, due to the proximity of the coronary sinus orifice and the presence at this site of intracardiac conduction tissue. At this point, the stitches must be placed parallel to the border of the ostium primum defect and must cause minimal tension because of the risk of injuring the conduction tissue. This is undoubtedly the most critical point of the operation. In twenty-six operations we had four cases of A-V block. This complication will be discussed later.

We have never observed any air embolism originating in the left cavities. Before the last two stitches are tightened, the anesthetist exerts positive pressure on the lung to empty the left auricle of the air it contains. This pressure is sufficient to ensure an adequate reflux of blood into the pulmonary veins thereby aiding the evacuation of the left cavities.

The end of the operation presents no particular difficulty. The right auricle is closed, the pericardium is left wide open and the pleura is drained. In cases in which a complete A-V block has occurred and persists at the end of the operation, the two electrodes of the electric stimulator are set in place, one on the right ventricular wall and the other in the parietal muscles.

Immediate and Late Results

Of the twenty-six patients we operated upon, six (23 per cent) died during or after the operation. These results are similar to the statistics published by others, e.g., Lillehei[4] reports nine deaths in his first series of twenty operations and five in a later series of seventeen operations,[1] Cooley[2] reports three deaths in eight operations and Kirklin[3,5] reports three deaths in eight operations. We believe that our casualties were the results of errors in the technic of perfusion and/or surgical repair. For this reason we should like to analyze them carefully.

Operative Deaths: Two deaths were directly attributable to the perfusion. One patient (Case 17) had anuria due to blood incompatibility (this was our first operation using extracorporeal circulation in 1955). In another patient (Case 18), an inadequate perfusion flow caused an irreversible cerebral anoxia with all the signs of decerebration, and the patient died within forty-eight hours. Today a longer experience with extracorporeal circulation enables us to avoid such mistakes.

Two other deaths were due to a tactical fault of the surgical repair. In one patient (Case 3), the Ivalon patch was not properly placed and interfered with the venous pulmonary return, provoking a massive pulmonary edema from which the patient died while on the operating table. In the other (Case 5), the repair of the atretic mitral ring was too tight and caused stenosis. As a result, pulmonary edema occurred and the patient died three days later.

With advances in technic such mistakes no longer occur. However, in two other cases (Cases 16 and 25), death still would have been unavoidable. The first patient (Case 16), a five year old child, died of massive pulmonary edema following closure of a mitral defect. The autopsy was unenlightening; the only possible explanation seemed to be a discrete stenosis of the aortic infundibulum. The other patient (Case 25) was a child with a single auricle. A complete A-V block occurred while the surgeon was partitioning the auricle. At first the patient reacted well to the administration of isoproterenol and electric stimulation, but after four days the reaction became gradually weaker and he died on the sixth day with every sign of an irreversible block and acute right heart failure.

Postoperative Complications: None of the other patients we operated upon had any serious postoperative complications. Preoperative pulmonary hypertension did not cause any serious postoperative complication. In one patient (Case 24) with a preoperative pulmonary pressure of 80/46 mm. Hg and a systemic pressure of 112/64, a small opening was made in the Ivalon patch placed on the ostium primum to act as a valve. Laboratory experiments had taught us that secondary closure of such small orifices occurs spontaneously. This precaution assured an uneventful postoperative course. In addition, the operative record of the pulmonary

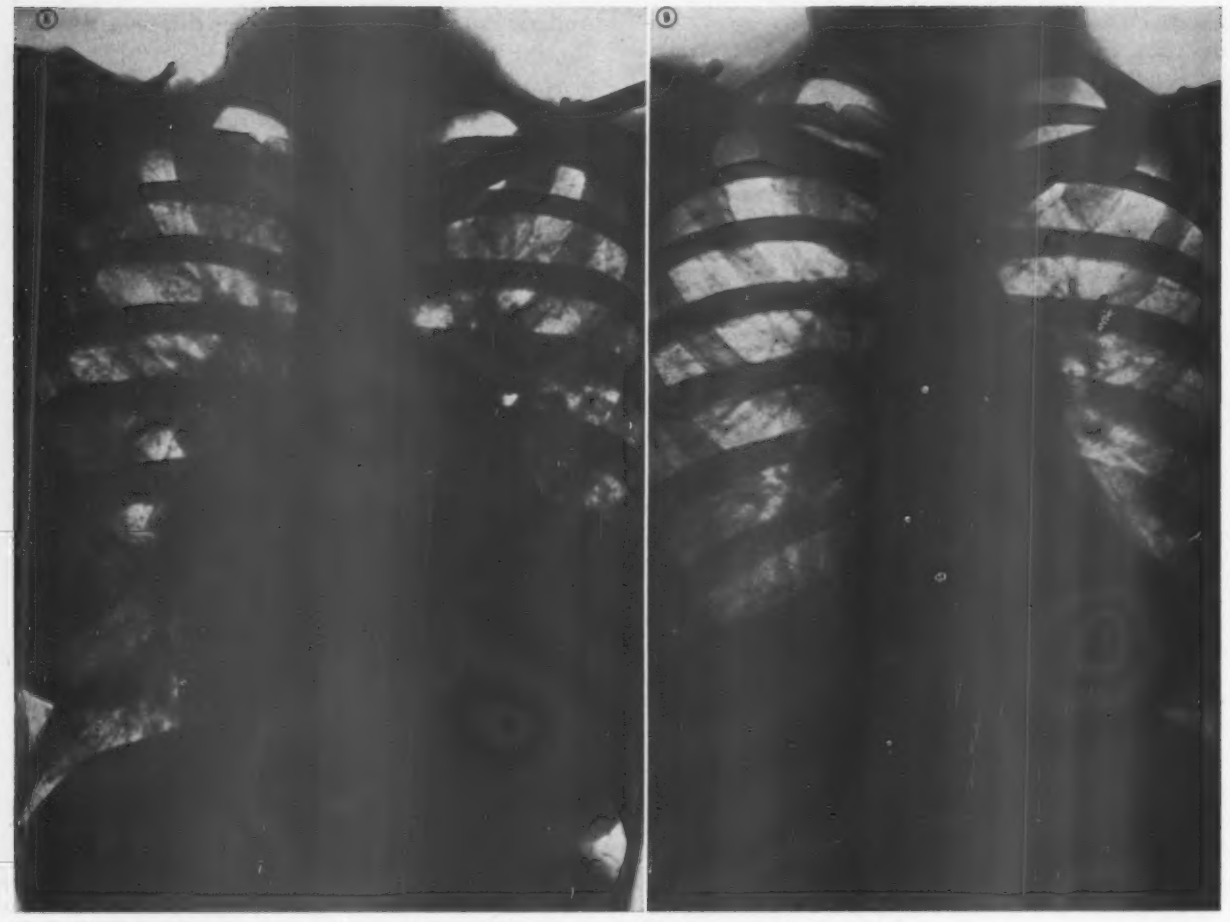


FIG. 3. Case 23. Ostium primum defect. Diminution of volume of the heart after operation. A, preoperative radiogram. B, radiogram ten months after operation.

pressure before and after the surgical repair had shown a marked fall of the pulmonary pressure. We believe that constant registering of the pressures during surgery is an important prognostic factor in dealing with a patient who suffers from pulmonary hypertension.

Two of the four patients with A-V block overcame this complication. In one sinus rhythm resumed after twelve hours of artificial electric stimulation (Case 7). In the other (Case 4) a complete block was still present but the ventricular rate was sufficiently rapid after a twenty-four hour perfusion of isoproterenol to enable him to withstand it without heart failure.

Late Results: Except for a few cases, we cannot yet evaluate the late results of surgery. Of the twenty patients who have survived it, fourteen were operated upon in the six months prior to the writing of this report and they have not been seen again; two were seen again five or ten months after surgery. One of these (Case 4), who had been operated upon for an A-V canal of the partial type, has remained practically symptom-free, the only clinical finding being a slight systolic murmur at the apex and a persistent A-V block with a ventricular rate of 56. The other (Case 24) presented a large ostium primum defect; he now leads a normal life despite a loud residual systolic murmur.

Four patients were catheterized again between six and twelve months after the operation: one with ostium primum (Case 23), two with A-V canal (Cases 1 and 2) and one with ostium secundum and a cleft of the mitral valve (Case 26). Figure 2 shows the results of cardiac catheterization. There was total disappearance of the shunt in three and subtotal in one, with the pulmonary pressure back to normal; in two of the three patients who had mitral insufficiency, the systolic murmur at the apex disappeared almost completely (Case 2 and 26). In the third case a grade 3 to 4 (scale of 10) murmur persists indicating a slight mitral insufficiency. In Case 23, the disappearance of the shunt was accompanied by a distinct decrease in heart size (Fig. 3).

These first hemodynamic results concern our earliest surgical cases. In the light of experience we trust that the results obtained in patients operated on more recently, who will return for cardiac catheterization, will be at least as good as the first ones. An adequate surgical repair of a formerly incurable defect now seems possible. Constant improvements in the technic of perfusion and repair should help to reduce the number of surgical casualties. However, the hard-to-anticipate risk of surgical trauma to the A-V conduction tissue remains, as does the difficulty of repairing certain complex valvular malformations.

Summary

This is a report of twenty-six patients with ostium primum and persistent common A-V canal who were operated upon.

Surgical anatomy is described. Although persistent common A-V canal is usually classified into complete and partial forms, we have observed several anatomic transitional varieties that represent the connecting link between the complete and partial forms; the valvular lesions are more variable than they are classically reported to be.

The operation was performed using extracorporeal circulation without induced cardiac arrest. The cleft in the mitral or tricuspid valve was repaired and the ostium primum defect was closed by suturing a piece of Ivalon sponge.

There were six deaths in this group of twenty-six patients: two were related to perfusion, two were caused by technical mistakes and two by complete heart block.

Addendum

Since this paper was submitted for publication, we have operated on six additional patients. The operations were performed using deep hypothermia below 10°C. with total circulatory arrest varying from thirty to forty-five minutes, obtained by a heart-lung machine connected with a heat exchanger.

Three patients with the complete form, in whom a total plastic repair of the mitral valve had been attempted, died.

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Persistent Atrioventricular Canal

Surgical Experiences

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WE HAVE operated on sixteen patients with common A-V canal. In all cases, the defect involved the lower part of the atrial septum and extended down through the atrioventricular ring to the upper part of the ventricular septum. All the patients had a defect in the annulus fibrosus, and both the tricuspid and mitral valves were cleft and deformed, producing regurgitation. The size of the ventricular septal defect varied. Four patients had large defects in the muscular ventricular septum in addition to having a defect in the membranous septum. Two patients had a narrow mitral ring, so that the filling of the left ventricle took place partly through the ostium and partly through the ventricular septal defect.

Physical examination showed a typical pansystolic apical murmur, indicating mitral regurgitation. The murmur was not always conducted to the left axilla, probably because the regurgitation occurred in the right auricle. This murmur can be recorded by esophageal phonocardiography.

An electrocardiogram with left axis deviation and reversed loop on the frontal vectorcardiogram was found in all the patients who were operated on. While a large auricular septal defect of secundum type with small lower rim cannot be distinguished from A-V commune at angiocardiography by left auricular injection, through injection into the left ventricle it is possible to show mitral insufficiency and eventual interventricular left-to-right shunt. More recently, a small injection into the left ventricle has been given, supplemented twenty to thirty minutes later with an injection into the left auricle.

OPERATIVE TECHNIC

In the first eight patients, the cleft of the valves was sutured and a prosthesis stitched into the defect above the valve-plane in the ventricular septal defect. In another three patients, a prosthesis was stitched into the defect below the valve-plane in the ventricular septal defect. In one patient, a prosthesis was also stitched into the cleft septal tricuspid cusp and, in another, into the mitral ring and valve to prevent the occurrence of mitral stenosis.

The last eight patients were operated on with a different technic. First, an annuloplasty was performed, according to the method of Senning, to repair the essential part of the malformation, supporting the valvular apparatus by repairing the defect in the annulus fibrosus (Fig. 1). A suture, which had been threaded through a small piece of Ivalon® sponge, was introduced through the anterior end of the annulus fibrosus; it passed just under the anterior valve and came out over the gap between the valves; thence, under the posterior valve into the posterior annulus fibrosus tissue. It was then threaded through a piece of Ivalon sponge and taken back by the same route. The suture was so tied that the ends of the annulus fibrosus approached each other; care was taken to avoid mitral stenosis. When the suture was drawn tight, the ventricular septal defect was reduced and it was possible to close the membranous defect with a few extra sutures.

In one case, an Ivalon sponge prosthesis was stitched into an atypical defect along the posterior ventricular wall. The supporting surfaces of the cleft mitral cusp facing each other were mutually adapted near the septum. (Stitching towards the free edge was avoided, since this could easily lead to mitral stenosis.)

The operation was performed in "anoxic cardiac arrest," and before the auricular septal defect was stitched, the mitral function was checked by removing the aortic clamp and allowing the heart to contract. The atrial septal defect was then closed. (In four cases, it was possible to do this without a prosthesis.)

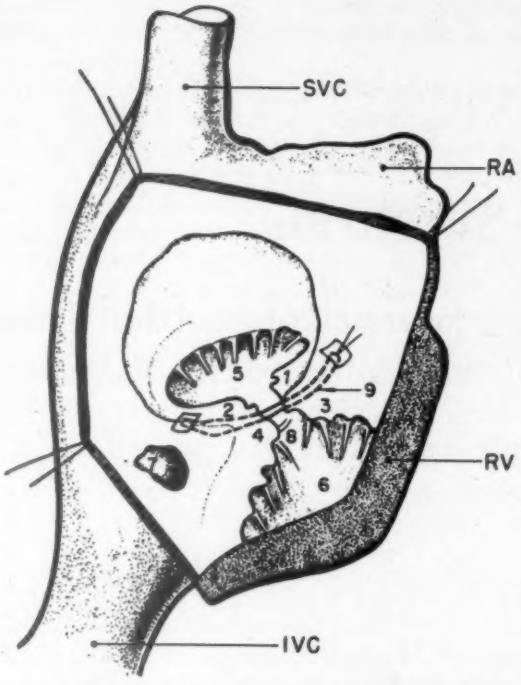


FIG. 1. Annuloplastic suture. 1-2, cleft mitral valve; 3-4, cleft septal cusp of tricuspid valve; 5, mitral orifice; 6, tricuspid orifice; 7, coronary sinus; 8, ventricular septum; 9, annuloplastic suture; SVC, superior vena cava, IVC, inferior vena cava; RA, right atrial appendage; RV, opened right ventricle.

The function of the tricuspid valve was then checked. In four patients on whom this operation was performed, the cleft septal tricuspid cusp was repaired.

Operative Results

Of the four patients with large muscular defects of the ventricular septum, one survived; she has signs of mitral insufficiency. One patient, in whom the mitral ring was widened with a prosthesis, had persisting mitral insufficiency; she died three months after operation from hemorrhage from gastric peptic ulcers. One patient could not be operated on, due to mitral stenosis; she died of A-V block. The fourth patient had anuria which was treated with dialysis; results were good, but she died suddenly after three weeks.

Of the twelve patients with defects in the membranous ventricular septum only, three died from A-V block; the others survived. Two patients have slight mitral insufficiency, one of whom has a 2-1 block. Three patients have had temporary A-V block postoperatively, which has undergone complete regression. Of the last eight patients, one with a large muscular ventricular septal defect died.

Summary

Sixteen patients with common A-V canal have been operated on, the last eight by a technic of annuloplastic suture. The over-all mortality was 37.5 per cent. Of the last eight patients operated on, only one died. The factors contributing to mortality were large muscular defects of the interventricular septum, persisting mitral insufficiency and postoperative A-V heart block.

Clinical Studies

A Myocardial Syndrome

With Particular Reference to the Occurrence of Sudden Death and of Premature Systoles Interrupting Antecedent T Waves*

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While the association of multiform premature systoles with organic heart disease is well established, little attempt has been made to describe the clinical and electrocardiographic features of a well defined syndrome[1] which occurs quite frequently in patients who exhibit multiform premature complexes and certain other arrhythmias. The purpose of this report is to describe examples of the syndrome, to note the frequency of occurrence of the associated phenomena of which it is composed, and to refer to a number of pathologic states in which many or most of the clinical features of the condition may be observed.

The features of the syndrome are as follows: (1) clinical evidence of myocardial damage; (2) interruption of the T wave before its completion, by a very premature QRS complex (the R on T phenomenon); (3) a high incidence of sudden death; (4) multiform ectopic ventricular complexes; (5) multiform ventricular complexes of supraventricular origin; (6) variability of the interval between successive ectopic complexes; (7) variability of the interval between the premature and the antecedent complexes; (8) ectopic complexes in runs of two or more, amounting in some cases to paroxysmal tachycardia; (9) T wave changes in complexes following a premature beat.

The frequency with which R on T waves occur clinically can be reduced or abolished by quinidine.[1] The occurrence of R on T waves may provide information concerning changes in the refractory period of the heart. It is a phenomenon which can be induced experimentally in a variety of ways[2–4] and is closely related to the occurrence clinically and in animal experiments of ventricular paroxysmal tachycardia, ventricular flutter and ventricular fibrillation.

Patients Studied

Information has been collected relating to eighty patients whose electrocardiograms showed the R on T phenomenon and some or all of the associated features referred to herein. The incomplete syndrome, lacking the R on T phenomenon, is quite common. In addition, published electrocardiograms have been examined for T wave interruption. Only exceptionally has the phenomenon been referred to by the authors of these papers.

Associated Cardiovascular Diseases: Table 1 indicates the cardiovascular diseases from which these patients suffered, together with the average age of patients with any one of these conditions. The table also includes the number of patients who died prior to January 1, 1959, the average survival time of those who died after the first recording of the R on T phenomenon and, finally, the number of deaths which were sudden in each group.

From this table it can be seen that: (1) The patients were elderly with the exception of those patients classified as having a "cardiomyopathy" and the one patient with the Wolff-Parkinson-White syndrome. (2) Most patients (90 per cent) had significant myocardial disease. Indeed, 25 per cent of these patients were suffering from congestive heart failure. In the remaining 10 per cent of patients, arrhythmia was the only evidence of cardiac abnormality.

The term cardiomyopathy has been used to designate conditions variously described as myocarditis and myocardosis. The diagnosis of myocarditis was made in three of the patients in this

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group on the basis of a significant arrhythmia subsequent to an illness which apparently damaged the myocardium.

Electrocardiographic Features: Table II indicates the relative incidence of the electrocardiographic features mentioned in the introduction. Emphasis is placed on the four main types of T wave interruption. The number of electrocardiograms showing any one of the particular features has been recorded. Two or more types of T wave interruption may, on occasion, occur in the same patient; hence in Table II the total number of electrocardiograms with various types of interruptions is greater than the total number of cases (eighty).

Abbreviations: In Table II, and subsequently, the following abbreviations have been used:

S by S refers to examples of ventricular complexes of supraventricular origin interrupted by other ventricular complexes of supraventricular origin (Fig. 1).

S by V refers to examples of ventricular complexes of supraventricular origin interrupted by ectopic ventricular complexes (Fig. 1).

V by S refers to examples of ectopic ventricular complexes interrupted by ventricular complexes of supraventricular origin.

V by V refers to examples of ectopic ventricular complexes interrupted by other ectopic ventricular complexes (Fig. 2).

TABLE I
Analysis of Eighty Cases

Diagnosis	No. of Cases	Average Age (yr.)	Sudden Deaths	Total Deaths	Average Survival Time Before Death (mo.)
Myocardial degeneration	37	68	11	27	17.4
Cardiac infarction	18	65	8	15	3.7
Hypertension	9	59	1	6	17.3
Cardiomyopathies	8	36	2	2	0.25
Thyrotoxicosis	2	56	0	0	—
Wolff-Parkinson-White syndrome	1	23	0	0	—
Mitral stenosis					
During valvulotomy	1	19	0	0	—
Spontaneous	1	36	0	1	1
Miscellaneous (Incidental arrhythmia)	3	47	0	0	—

RESULTS

T WAVE INTERRUPTION

On the basis of selection all electrocardiograms showed T wave interruptions. The T wave may be interrupted in four main ways. A complex of supraventricular or ventricular origin may be interrupted by either a supraventricular or a ventricular premature complex. Interruptions of the S by V and V by V types were more common than the S by S and V by S types. The former types were found in 82 per cent of the electrocardiograms, the latter in only 28 per cent. This relative frequency is to be expected as ventricular premature systoles are the more common and the supraventricular type of interruption is less likely to occur because of delay in conduction at the A-V node.

There was no difference in the frequency of V by V and S by V types of interruptions. However, of the supraventricular type of interruptions only one example of the V by S form was found. The V by S type of interruption was uncommon, for this requires either

TABLE II
Relative Frequency of the Various Electrocardiographic Features

Origin of Interrupting Complex	Type of Interruption	Number of Electrocardiograms Showing each Type of T Wave Interruption	Multiform Ectopic Ventricular Complexes	Multiform Ectopic Supraventricular Complexes	Variability of Interval Between the Premature and Antecedent Complex	Ectopic Complexes in Runs of Two or More (including paroxysmal tachycardia)	Variability of Interval Between Successive Ectopic Complexes
Ventricular (sixty-six electrocardiograms)	V by V	42	58	16	54	48	36
	S by V	42					
Supraventricular (twenty-four electrocardiograms)	S by S	24	9	18	10	10	7
	V by S	1					

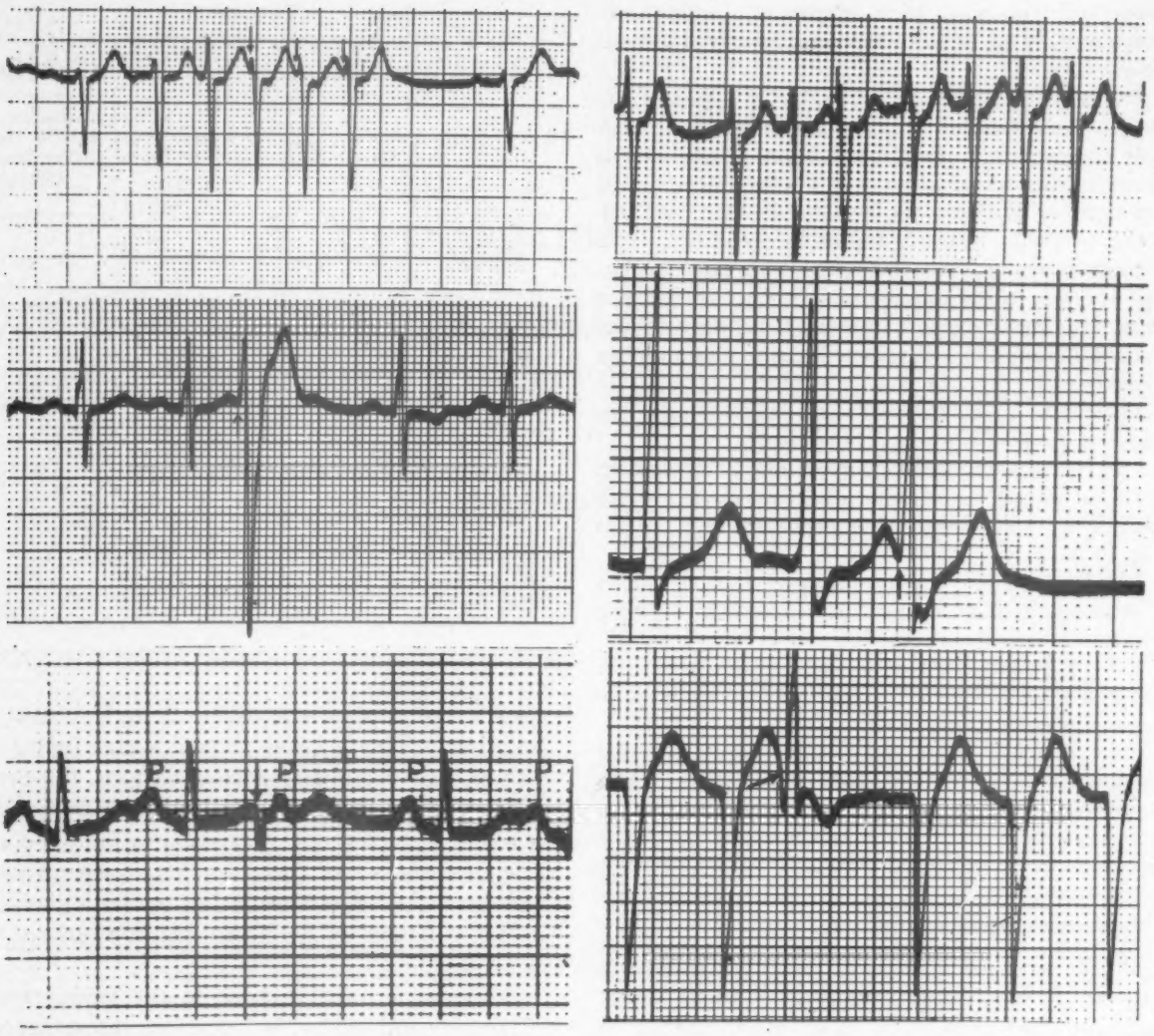


FIG. 1. Top tracings show S by S type interruptions (lead V_2) occurring during auricular fibrillation (paroxysmal in the left tracing). A degree of aberration in the ventricular conduction of these supraventricular complexes may be seen. Middle left tracing demonstrates S by V type interruption (lead V_2) with postextrasystolic T wave change in a patient with ischemic heart disease. Middle right tracing (Case 7) shows S by S type interruption (lead V_4) due to a premature supraventricular systole. Aberration in the ventricular conduction of this complex may be seen. Lower tracings demonstrate S by V type interruptions in patients with ischemic heart disease. In all tracings arrows mark the sites of interruption.

interruption of a very late interpolated ventricular extrasystole, or the interruption of a ventricular systole by a succeeding supraventricular premature systole. Of the twenty-four examples of supraventricular type interruptions (S by S), eleven were due to premature supraventricular beats; fifteen cases were due to rapid auricular fibrillation. Two tracings showed both forms, the auricular fibrillation being paroxysmal.

OTHER ELECTROCARDIOGRAPHIC FEATURES

Of the sixty-six electrocardiograms which showed ventricular types, that is, V by V or S by V interruptions, all but eight showed multiform ventricular complexes in addition, and all but twelve showed some variability of the interval after the preceding sinus beat (Fig. 3). In forty-eight of these sixty-six electrocardiograms ectopic complexes occurred in runs of two or more and in the majority of these (thirty-six) there was a variation in the interval between successive ectopic complexes. Instability of the myocardium was further demonstrated by seven of these patients having a paroxysm of ventricular tachycardia. Of the twenty-four electrocardiograms which showed supraventricular type interruptions, all but six showed multiform ventricular complexes of supraventricular origin. About half showed

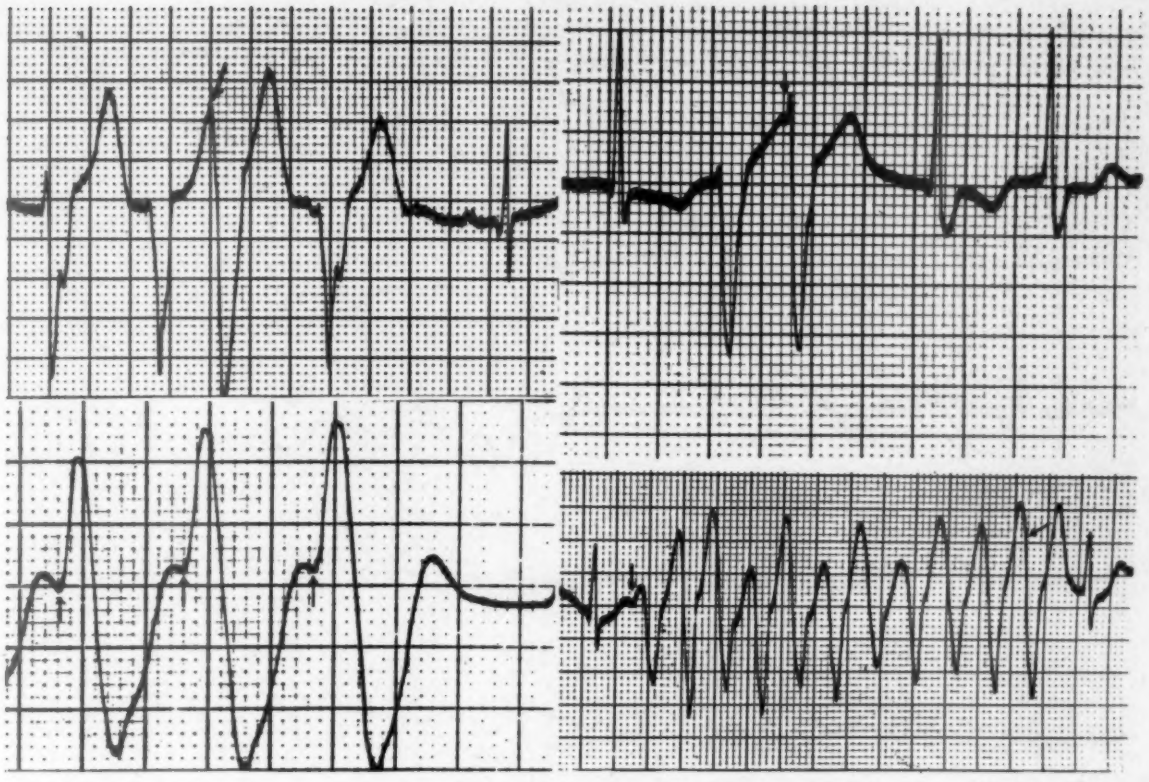


FIG 2. Upper left tracing shows V by V type interruption (lead III) recorded during cardiac catheterization when the catheter was in the right ventricle. The T wave of the second ventricular complex has been interrupted before its summit. Upper right tracing shows V by V type interruption (lead V_5) occurring in a patient with ischemic heart disease. Note the postextrasystolic T wave inversion. Lower left tracing reveals V by V type interruption (lead I) occurring during a paroxysm of ventricular tachycardia which followed a myocardial infarction. The appearances of T wave interruption are confirmed in such a case by noting the form of the uninterrupted T wave of the end complex. Lower right tracing (Case 6) shows a paroxysm of ventricular tachycardia (lead V_4) occurring in a patient who dated his symptoms of palpitations from an attack of "Asian Flu." The paroxysm begins with an S by V interruption and V by V interruptions follow. In all tracings arrows mark the sites of interruption.

variability of the interval between successive beats and the occurrence of complexes in runs of two or more. Three of the tracings showed paroxysmal auricular tachycardia.

The frequent association of multiform ventricular complexes with multiform supraventricular complexes is to be noted though the latter may not be causing T wave interruption. Conversely, when supraventricular complexes are responsible for the T wave interruption, multiform ventricular ectopic beats may also be found in the tracing.

In approximately 15 per cent of electrocardiograms, alteration in the form of the T wave in one or more post-extrasystolic complexes was noted (Figs. 1 and 2).

PATHOLOGIC STATES ASSOCIATED WITH T WAVE INTERRUPTION AND SUDDEN DEATH

Classification into eight groups was based on the dominant cardiovascular disability from which the patient suffered (Table I). Of eighty patients in this series, fifty-one died; however, many patients could well have been expected to die at any time from myocardial disease or in some cases from "old age." Nevertheless, the occurrence of sudden death in twenty-two of the fifty deaths raises the question of a sequential relationship between T wave interruption and sudden death, which will be discussed later.

Myocardial Degeneration and Hypertensive Heart Disease: These two categories have been considered together. The term myocardial degeneration has been used to describe a group of patients whose disability appeared to be chronic myocardial ischemia. The great majority were elderly.

Of the forty-six patients in these two categories, thirty-three died within an average of

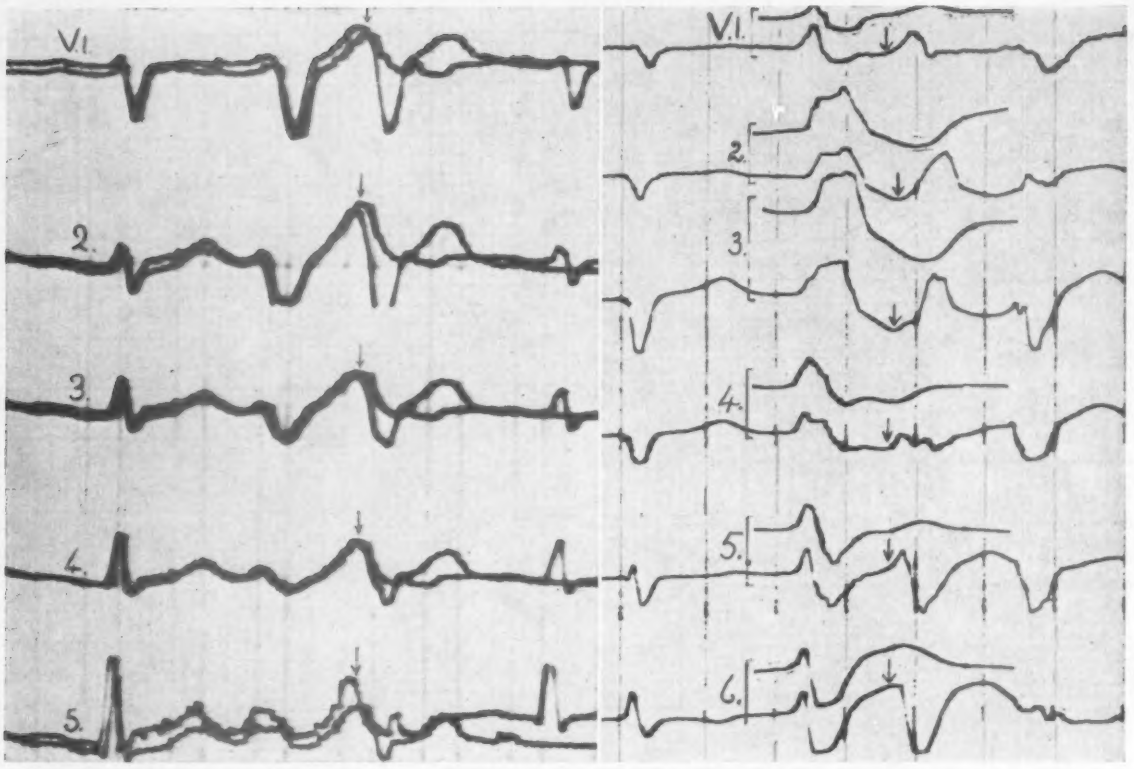


FIG. 3. These tracings, in which several precordial leads were recorded, simultaneously show T wave interruption of the V by V type occurring in the chest leads. In the left tracing complexes showing the interruptions have been superimposed on similar uninterrupted complexes. The right tracing is a further example, but here examples of the uninterrupted complexes have been inserted above similar interrupted complexes. Arrows mark the sites of interruption. The vertical lines mark time intervals of 0.2 second.

17.4 months after the phenomenon of T wave interruption was recognized. Twelve of these patients died suddenly.

Cardiac Infarction: Eighteen patients had experienced a myocardial infarction. Of this number, fifteen patients died within an average of 3.7 months after the T wave interruption was recognized. Eight of these deaths were sudden.

Cardiomyopathies: This is a small but interesting group (Table III) comprising patients ordinarily described as having myocarditis or myocardosis. In addition to our personal cases, a survey of the literature of cardiomyopathies has been made and reference is given to published electrocardiograms from such cases in which we have been able to find examples of the R on T phenomenon. The clinical conditions which led to damage of the myocardium are indicated below.

Fiedler's myocarditis: Case 1. A sixty-eight year old woman was admitted to the hospital suffering from Stokes-Adams syndrome. Partial and, later, complete heart block occurred with premature systoles causing S by V and V by V types of interruptions. The patient died suddenly following ventricular flutter. At postmortem a diagnosis of Fiedler's myocarditis was confirmed.

An idiopathic, febrile myocarditis (possibly Fiedler's): Case 2. This patient, a twenty-one year old man who was a school teacher, was seen by the courtesy of the physicians of the Mahatma Ghandi Medical College in Indore. He had had palpitations and congestive heart failure for seven years. At different times supraventricular tachycardia, auricular fibrillation, auricular flutter, all types of premature systoles and first and second degree heart block had been recorded. The T wave interruption was of the S by S type.

Rheumatic myocarditis: Case 3. An emaciated thirteen year old boy with congestive heart failure, mitral stenosis and mitral regurgitation was seen by the courtesy of Professor Roy of the All India Institute of Medical Sciences in New Delhi. In the electrocardiogram, which demonstrated auricular fibrillation, a very early interruption occurred 0.3 second after the antecedent R wave. The shortest cycle length was 0.5 second and the longest nearly 0.6 second.

Influenza: Cases 4, 5 and 6. Of these three patients who had cardiomyopathy following influenza, one recovered completely from the arrhythmia and

TABLE III

Clinical and Electrocardiographic Details of Patients Who Showed the R on T Phenomenon. Cases of "Myocardial Degeneration," Infarction and Hypertensive Heart Disease Have Not Been Included

Case	Sex and Age (yr.)	Type of Interruption: S by S	S by V	V by S	V by V	Polymorphic Ectopic Ventricular Complexes	Variability of Interval After Antecedent Beat	Ectopic Ventricular Complexes in Runs of Two or More	Variability of Interval Between Successive Beats	Polymorphic Ventricular Complexes of Supraventricular Origin	Types of Rhythm Encountered and Electrocardiographic Evidence of Myocardial Damage	Clinical Features	Progress of Patient*	Survival Time of Patients Who Died
1	F, 68		+		+	+	+	+	+		Partial and later complete heart block; ventricular flutter	Fiedler's myocarditis confirmed postmortem; Stokes-Adams attack	DS	Died same day
2	M, 21	+									Supraventricular tachycardia; auricular flutter and fibrillation; heart block; auricular and ventricular premature systoles	Cardiac enlargement; congestive heart failure for several years	S	
3	M, 13	+									Auricular fibrillation	Rheumatic fever with mitral stenosis and regurgitation	S	
4	F, 23				+	+	+	+	+		Premature ventricular systoles	Breathlessness	S	
5	F, 60		+			+	+				Premature ventricular systoles	Palpitations following Asian influenza	S	
6	M, 26		+		+		+	+	+		Premature ventricular systoles; paroxysmal ventricular tachycardia	Palpitations and dizziness following Asian influenza	S	
7	M, 14	+				+	+	+			Multiple premature auricular and ventricular systoles	Asymptomatic; pulse irregularity detected during convalescence from poliomyelitis	S	
8	M, 23		+				+				Uniform premature ventricular systoles	Asymptomatic Wolff-Parkinson-White syndrome	S	
9	M, 67		+		+			+			Auricular tachycardia (1:1) and later (2:1) block; ventricular paroxysmal tachycardia	Hemochromatosis; congestive heart failure; megaloblastic anemia; myocardial fibrosis confirmed postmortem	DS	18 days
10	F, 68		+			+	+	+	+		Premature ventricular systoles; A-V dissociation with auricular flutter; T wave inversion in lead I.	Coronary thrombosis confirmed postmortem	DG	
11	F, 78	+								+	Paroxysmal auricular fibrillation and heart block	Cardiac enlargement and hypostatic pneumonia	D	Same day
12	M, 68		+		+	+	+	+	+		Intermittent heart block; premature ventricular systoles; posterior infarction pattern	Cardiac infarction	S	4½ years
13	F, 70		+			+	+			+	Premature ventricular systoles; intermittent A-V block; ischemic changes	Palpitations and blackouts	DS	5 years
14	F, 32				+	+	+	+	+		Auricular and ventricular premature systoles; complete heart block; ventricular paroxysmal tachycardia; ventricular flutter and fibrillation (recurrent)	Stokes-Adams attacks for five years	DG	About 3 years
15	F, 62				+	+	+	+	+		Premature ventricular systoles; heart block; short run of ventricular flutter	Stokes-Adams attacks for five years	DG	7 years
16	F, 56	+				+	+	+			Supraventricular premature systoles	Thyrotoxicosis (lowest basal metabolic rate, + 32); labile hypertension; slight cardiac enlargement	S	
17	M, 56		+								Paroxysmal auricular fibrillation; biphasic T waves in leads I and II	Thyrocardiac symptoms improved by thyroidectomy	S	

* S = Survived; D = Died; DS = Died suddenly; DG = Died gradually.

details have been published previously.[1] The other two patients were seen recently and both related the onset of their symptoms of palpitations to an attack of "Asian influenza" some months previously. One of these patients, a previously fit man of twenty-six years (Case 6), was observed during several short paroxysms of ventricular tachycardia following exercise. Both patients were relieved of their symptoms by quinidine (Fig. 2, lower right tracing).

Poliomyelitis: Case 7. A boy fourteen years old had poliomyelitis. Five months after admission irregularity of his pulse was noted and a subsequent electrocardiogram showed auricular premature systoles with T wave interruption and aberration of the ventricular conduction of these supraventricular impulses. Two years later these abnormalities were still present but the patient had no cardiac symptoms. He has had no treatment for the arrhythmia (Fig. 1, middle right tracing).

Hemochromatosis: Case 9. One patient, a man aged sixty-seven years, with hemochromatosis is included. Myocardial fibrosis was found on postmortem examination. Interruptions of the S by V and V by V type were recorded together with ventricular paroxysmal tachycardia. This patient died suddenly.

Chagas' disease: We have not personally observed patients with this disease, but premature beats are commonly described. Rosenbaum and Alvarez[5] make the statement that "ventricular premature beats were present in eight out of ten patients who died within the first two years of the observations; all of them died suddenly." In the electrocardiograms published by these authors, V by V type interruptions may be seen (Ref. 5, Fig. 19, lead V_5).

Sarcoidosis: In this disease sudden death has been reported with postmortem studies revealing involvement of the heart.[6,7] At least one report[8] of a patient who died suddenly with sarcoid involvement of the heart includes an electrocardiogram which shows probable T wave interruption (Ref. 8, Fig. 4) associated with multiform premature ventricular systoles and transient ventricular tachycardia.

Dystrophia myotonica: T wave interruption has been described among the various electrocardiographic manifestations of this disease and an example has been published[9] (Ref. 9, Fig. 4, leads III and aVF).

Thyrotoxicosis: Two thyrotoxic patients (Cases 16 and 17) are included in this series. In both cases the T wave interruption was of the S by S type. The underlying arrhythmia in one was auricular fibrillation, in the other, supraventricular premature systoles. Both patients survived.

Wolff - Parkinson - White Syndrome: Case 8. An asymptomatic young man, twenty-three years of age, was found to have the Wolff - Parkinson-White syndrome, an electrocardiogram having been taken because of irregularity of his pulse. Although the ventricular ectopic impulses were uniform in shape, there was a variability of the interval between the ectopic complex and preceding sinus beat. Exercise produced T wave interruption of the S by V type. This patient has remained fit.

Sudden death may occur in patients with the Wolff - Parkinson - White syndrome.[10] T wave interruption may be seen in electrocardiograms published[11] to illustrate pseudoventricular tachycardia and pseudoventricular fibrillation in this condition (Ref. 11, Fig. 3, lead III particularly).

An electrocardiogram showing paroxysmal ventricular tachycardia produced during the cardiac catheterization of a patient[12] with Wolff-Parkinson-White syndrome also shows T wave interruption. (Ref. 12, Fig. 2, upper tracing, leads II and III.)

Mechanical Irritation of the Heart During Surgical and Diagnostic Procedures: Both personal experience and published electrocardiograms indicate that the R on T phenomenon may occur when the heart is subjected to manipulative procedures. An example of T wave interruption during mitral valvulotomy has been included and reference may be made to further examples[13] recorded during this operation (Fig. 3, strips 4, 5 and 6). In addition, procedures such as pericardiectomy[14] (Ref 14, Fig. 2b in which the second of three ventricular ectopic complexes is interrupted) and the operation for pulmonary stenosis[15] (Ref. 15, Fig. 3, b and c; also Fig. 4), have caused T wave interruption.

T wave interruption may also be seen during cardiac diagnostic procedures. It has been noted frequently during cardiac catheterization in this department (Fig. 2, upper left tracing) and a further example in a published series[16] may be seen (Ref. 16, Fig. 5, second tracing, interruption of the first complex). T wave interruption may also occur during angiocardiography[17] (Ref. 17, Fig. 3, Case 3, at 5, 9.5 and 11.5 minutes), and during ventricular puncture[18] (Ref. 18, Fig. 4: several V by V types of interruptions during a paroxysm of ventricular tachycardia).

Auricular Fibrillation: A rapid auricular fibrillation may produce T wave interruption of the S by S type. Fifteen examples have been found and included in the series. Eleven of these patients died within an average of nine teen months after the phenomenon was recorded.

Two of these deaths were sudden (Fig. 1, upper two tracings).

Heart Block: In this series, eight of the electrocardiograms showing T wave interruption were associated with heart block. The etiologic background of the conduction disturbance varied, and some of the cases are also included elsewhere under appropriate headings. Three of these patients had had definite Stokes-Adams attacks and an electrocardiographic record of ventricular flutter or fibrillation was obtained in each of the three. Two of these three died suddenly. Details are indicated in Table III.

In all cases except one, the type of interruption was, as would be expected, of the V by V or S by V type, the latter being found only when the block was intermittent.

Eight papers[19–26] in which the reproduced electrocardiograms of Stokes-Adams attacks showed T wave interruptions were found without difficulty. When the cause of Stokes-Adams attacks is ventricular fibrillation or flutter, the frequency with which there is associated T wave interruption is striking. Such interruption is usually of the V by V type, being due to multiform ventricular premature systoles.

Drug-Induced T Wave Interruption: A number of patients in this series were receiving digitalis and probably the multiform premature ventricular systoles and associated T wave interruptions which were encountered were due to this drug. In several instances digitalis was withheld with the result that the R on T phenomenon disappeared.

Procaine amide[27] may produce premature ventricular systoles and ventricular tachycardia with T wave interruption. Fuadin® may have the same effect[28] and T wave interruption can be seen during a bigeminal rhythm which occurred during the parenteral administration of reserpine[29] (Ref. 29, Case 2, lead II).

Comments

Interruption of the T wave by the succeeding premature QRS complex is a phenomenon of considerable physiological interest and clinical importance. In order to establish that T wave interruption has occurred, measurement of the T wave must be made with care. Errors in measurement of the termination of the T wave have been pointed out by Lepeschkin and Surawicz.[30] T wave interruption is not uncommon but, as with any phenomenon of an intermittent character, recognition depends largely upon the zeal in searching for it.

Interest in the phenomenon of T wave interruption followed the observation (by Fastier and Smirk[2]) that T wave interruption might be observed experimentally during the phase of chaotic rhythm preceding ventricular flutter induced by epinephrine given after amarin (2:4:5-triphenyl dihydro-imidazole). This led to a clinical search for the phenomenon with the result that reports of seventeen cases were published the next year.[1] Five of the patients had died at the time of publication and three of these deaths had been sudden. In the present series twenty-two of fifty-one recorded deaths were sudden. Since that time Lepeschkin and Rosenbaum[31] have also associated T wave interruption with serious heart disease. Scherf and Schott,[32] in their book on extrasystoles, note the occurrence of T wave interruption. They quote Rothberger[33] as observing T wave interruption by interpolated extrasystoles and interpreting this observation as evidence that the endogenous stimulus strength leading to the extrasystole must in these cases be considerable. Otherwise, scant reference has been made to T wave interruption. In contrast, many published electrocardiograms portray the phenomenon, although specific comment is not made by the authors.

T wave interruption as observed in the electrocardiogram may be interpreted as being spatial or temporal. A spatial interpretation implies that a portion of the ventricular myocardium has recovered prematurely and is capable of propagation, while other areas are still undergoing repolarization and are still contributing to the electrical potentials of the T wave.

In contrast, the temporal view is that the myocardium may be capable of propagating an impulse even though it is not fully repolarized. Evidence that such a phenomenon may occur was obtained by Fastier and Smirk[2] in their experiments with amarin in which T wave interruption was on occasion recorded by a local electrogram.

Clinically, T wave interruption is usually associated with significant heart disease, as for example acute and chronic myocardial ischemia, hypertensive heart disease and such cardiomyopathies as Fiedler's myocarditis, Chagas' myocarditis and influenzal myocarditis.

T wave interruption occurring during the acute stage of myocardial infarction probably indicates an added danger to the patient. Sudden death may occur and, as a number

of patients who had R on T waves have been observed during attacks of ventricular tachycardia, flutter and fibrillation, ventricular fibrillation may have been the cause of the sudden deaths. When recovery from cardiac infarction occurs the eventual prognosis may not be adversely affected.

Of particular interest is T wave interruption occurring during the course of diseases associated with a cardiomyopathy. The association of myocarditis and myocardosis with sudden death has been well documented. Unfortunately, this correlation has usually been on the basis of postmortem rather than electrocardiographic studies.[34,35] In electrocardiographic studies of various types of myocarditis, arrhythmias have been documented in only a small percentage of the cases. However, a striking exception is found in chronic Chagas' myocarditis.[5] Nevertheless, where electrocardiograms have been published the association of T wave interruption and subsequent death has been noted by us in several publications. The frequency with which heart block and T wave interruption are associated at least suggests that the latter phenomenon may be related to the precipitation of ventricular fibrillation and its clinical manifestation, Stokes-Adams attacks.[36–39]

The production of T wave interruption during surgical and diagnostic procedures is also of interest, because all such procedures have been known to cause fatal arrhythmias. Septal stimulation is likely during cardiac catheterization and during angiocardiography. Experimentally, septal stimulation will produce T wave interruption.[4]

There may be a relationship between ventricular fibrillation occurring in association with T wave interruption and the vulnerable period. The vulnerable period is a brief interval occurring in late systole during which an electrical shock of suitable intensity may precipitate ventricular fibrillation. The objection to the drawing of a direct analogy between an artificial stimulus producing ventricular fibrillation when applied during the vulnerable period and a very premature spontaneous systole having the same effect, has been that an effective artificial stimulus needed to be several hundred times the threshold strength.[40] However, if the stimulus is applied accurately during the period of relatively enhanced excitability described by Hoffman et al.,[41] or if the area stimulated is in the wake of the excitation wave (Palmer[4]), stimuli which are only a few times greater than the diastolic threshold may precipitate ventricular fibrillation.

Because of the poor prognosis associated with T wave interruption, therapy has been given as soon as the phenomenon has been recognized, or when the electrocardiogram has shown related features such as multiform ventricular systoles. Quinidine and procaine amide in adequate doses have almost invariably abolished the interruptions even though occasional ectopic beats may still be apparent in the tracing.

Summary

Eighty cases of a well defined myocardial syndrome, an important feature of which is the interruption of T waves by premature QRS complexes, are reported. Other features of the syndrome include myocardial damage and sudden death, multiform premature ventricular complexes, aberration in the form of ventricular complexes of supraventricular origin, variation in the interval between successive ectopic complexes and the preceding sinus complex and ectopic complexes in runs of two or more. Post-extrasystolic T wave changes are sometimes observed.

The R on T phenomenon is by no means uncommon when looked for, and it may be seen in a wide variety of pathologic states involving the heart, such as myocardial infarction, ischemic heart disease, hypertensive heart disease and several distinct myocardiopathies. It may also be seen during cardiac surgery and during diagnostic procedures such as cardiac catheterization, angiocardiography and ventricular puncture.

The phenomenon may be suspected clinically when very premature beats are noted on auscultation, and it is frequently found in electrocardiograms recording such arrhythmias as multiform ventricular systoles, ventricular tachycardia, flutter and fibrillation, auricular paroxysmal tachycardia and auricular fibrillation.

The incomplete syndrome without T wave interruption is very common and, frequently, further observation and electrocardiography will reveal the missing features.

The syndrome is frequently associated with sudden death and prophylactic administration of quinidine is recommended as a therapeutic measure.

Acknowledgment

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Heart Sounds and Murmurs in Arterial Hypertension*

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SINCE the advent of phonocardiography, considerable attention has been given to the adequate registration of heart sounds and murmurs; however, very little has been written about the recording of the stethoscopic findings in arterial hypertension. Previous investigations of the graphic characteristics of heart sounds and murmurs in hypertensive patients were carried out without the benefit of suitable filtering and amplifying procedures. Modern electronic devices allow a more precise and accurate recording of these auscultatory events. It is the purpose of this study to present, by our method of phonocardiography, a comprehensive analysis of the heart sounds and murmurs in patients with hypertension.

CASE MATERIAL

Forty-three patients with moderate to severe arterial hypertension were selected for phonocardiography from the wards of a large general hospital. They were included in the study when their recumbent diastolic blood pressure was consistently 110 mm. Hg or above. Of these forty-three patients with hypertension, three had chronic glomerulonephritis and the remainder had essential benign hypertension. The patients had a complete history and physical examination, complete blood count, urinalysis, serology, chest x-ray, and electrocardiogram. Almost all the patients had been referred to the hypertensive-nephritic service of the hospital for diagnostic workup and treatment. None of the forty-three patients had a history or evidence of rheumatic fever, syphilitic aortic disease, congenital heart disease or significant anemia.

The forty-three patients were divided into three groups based on the presence of left ventricular hypertrophy or the finding of a faint basal diastolic murmur:

Group I consisted of twelve patients with no evidence of left ventricular hypertrophy on physical examination, electrocardiogram or posteroanterior chest roentgenogram and without the auscultatory finding of a basal diastolic murmur. Two of the twelve were being maintained on digitalis because of a past episode of congestive heart failure; however, at the time of their phonocardiographic study there was no evidence of cardiac insufficiency.

Group II was comprised of sixteen patients who also had no evidence of a diastolic murmur at the base of the heart on physical examination; however, they did have left ventricular hypertrophy on physical examination, electrocardiogram and chest roentgenogram. Ten patients in this group had a past history of congestive heart failure on at least one occasion; they were being maintained on digitalis at the time of phonocardiography. Of the remaining six patients in group II, two had mild exertional dyspnea and four were free of cardiovascular symptoms.

Group III consisted of fifteen patients who had, on auscultation, an early diastolic murmur at the base of the heart; we believe that this murmur was due to insufficiency of the aortic valve. All the patients in this group had left ventricular hypertrophy on physical examination, electrocardiogram and posteroanterior chest roentgenogram. None of these patients had the peripheral vascular manifestations of aortic insufficiency. Two had minimal dilatation of the aorta on chest roentgenogram (posteroanterior projection). Nine patients had had the clinical manifestations of congestive heart failure in the past and were being maintained on digitalis at the time the phonocardiogram was recorded. A tenth patient had dyspnea on exertion; he was not receiving digitalis at the time of the sound tracing. The remaining five patients did not exhibit evidence of congestive heart failure on physical examination.

Control Series: Nineteen persons without evidence of heart disease were selected from hospital personnel

* From the Department of Internal Medicine, Cardiovascular Section, Marquette University School of Medicine, and the Milwaukee County Hospital, Milwaukee, Wisconsin. This study was carried out during Dr. Puchner's tenure as a Research Fellow of the Wisconsin Heart Association.

† Present address: Laboratory of Physiological Hygiene, University of Minnesota, Minneapolis, Minnesota.

TABLE I
Findings in Forty-Three Hypertensive Patients

Case No.	Age (yr.), Sex, Race	Blood Pressure (Recumbent) (mm. Hg)		Heart Rate	Q-1 Interval (sec.)	First Sound (sec.)		Second Sound (sec.)		Third Sound Apex	Fourth Sound Apex	Murmurs*
		Systolic	Diastolic			Aortic Area	Apex	Aortic Area	Apex			
Group I. Hypertension Without Left Ventricular Hypertrophy and Without Aortic Insufficiency												
1†	36, F, N	210	140	84	0.06	0.12	0.14	0.08	0.06	...	Present	None
2†	63, M, N	160	110	82	0.07	0.13	0.16	0.07	0.06	...	...	None
3	45, M, W	190	130	68	0.06	0.14	0.16	0.07	0.06	...	...	None
4	26, F, N	170	120	60	0.06	0.13	0.16	0.06	0.05	...	...	None
5	51, F, N	160	110	62	0.05	0.10	0.14	0.07	0.06	...	...	Grade 1, SM, aortic
6	42, F, N	180	115	83	0.06	0.10	0.11	0.08	0.06	...	Present	Grade 2, SM, aortic
7	60, F, N	210	110	79	0.06	0.12	0.13	0.07	0.07	...	...	Grade 2, SM, apex
8	53, F, N	165	125	100	0.06	0.12	0.14	0.07	0.05	...	...	Grade 1, SM, aortic
9	36, M, N	160	115	60	0.05	0.13	0.13	0.06	0.06	...	...	Grade 1, SM, apex
10	43, F, W	185	120	80	0.06	0.12	0.12	0.07	0.06	...	...	Grade 2, SM, apex
11	50, M, W	190	110	90	0.06	0.12	0.13	0.06	0.05	...	...	Grade 1, SM, apex
12	41, M, W	190	125	79	0.05	0.13	0.13	0.06	0.05	...	...	Grade 1, SM, apex
					(0.06)‡	(0.12)	(0.14)	(0.07)	(0.06)			
Group II. Hypertension with Left Ventricular Hypertrophy but Without Aortic Insufficiency												
13†	44, M, W	220	125	50	0.07	0.12	0.14	0.08	0.08	...	...	None
14	38, M, W	260	150	77	0.06	0.17	0.18	0.08	0.06	...	...	None
15†	59, F, N	240	130	80	0.07	0.09	0.10	0.08	0.07	...	Present	Grade 3, SM, aortic
16	48, F, W	250	140	86	0.05	0.11	0.12	0.08	0.06	...	Present	Grade 2, SM, pulmonic
17†	45, M, W	200	120	74	0.05	0.12	0.12	0.08	0.06	...	...	Grade 2, SM, pulmonic; PSM, apex
18†	68, F, W	220	110	67	0.06	0.12	0.13	0.08	0.06	Present	Present	Grade 2, SM, aortic
19†	44, M, W	180	120	83	0.07	0.12	0.13	0.07	0.07	Present	Present	Grade 1, SM, aortic; Grade 1, SM, apex
20†	55, M, W	220	140	72	0.04	0.10	0.12	0.07	0.06	...	Present	Grade 3, SM, apex
21†	80, M, W	240	130	65	0.04	0.10	0.10	0.07	0.05	...	...	Grade 3, SM, aortic; Grade 3, SM, apex
22†	44, M, N	170	140	66	0.07	0.12	0.12	0.09	0.08	Present	...	Grade 4, SM, apex; PSM, apex
23†	56, M, N	210	110	47	0.07	0.16	0.18	0.09	0.06	...	...	Grade 1, SM, apex
24	42, M, N	175	125	83	0.07	0.14	0.17	0.08	0.07	...	Present	Grade 2, SM, pulmonic; systolic click, aortic
25	49, M, N	180	120	57	0.06	0.14	0.16	0.07	0.06	...	...	Grade 2, SM, apex
26	39, F, N	215	125	100	0.06	0.12	0.15	0.08	0.07	Present	...	Grade 3, SM, pulmonic Grade 2, SM, apex
27†	59, F, W	180	115	75 (atrial fibrillation)	0.07	0.10	0.13	0.09	0.07	Present	...	Grade 2, SM, apex
28	49, F, W	200	120	79	0.07 (0.06)	0.12 (0.12)	0.14 (0.14)	0.08 (0.08)	0.06 (0.07)	...	...	Grade 2, SM, apex

(Continued on next page)

TABLE I (*Continued*)
Findings in Forty-Three Hypertensive Patients

Case No.	Age (yr.), Sex, Race	Blood Pressure (Recumbent) (mm. Hg)		Heart Rate	Q-1 Interval (sec.)	First Sound (sec.)		Second Sound (sec.)		Third Sound Apex	Fourth Sound Apex	Murmurs*
		Systolic	Diastolic			Aortic Area	Apex	Aortic Area	Apex			
Group III. Hypertension with Both Left Ventricular Hypertrophy and Aortic Insufficiency												
29†	72, M, W	240	110	70	0.08	0.15	0.16	0.08	0.09	...	Present	Grade 1, SM, 3PL; DM, aortic
30†	41, M, W	210	140	81	0.09	0.12	0.14	0.09	0.09	Present	...	Grade 1, SM, 3PL; DM, 3PL; PSM, apex
31†	74, F, W	200	110	97	0.08	0.12	0.13	0.08	0.07	Present	...	Grade 2, SM, 3PL; DM, aortic
32	48, M, N	260	150	94	0.06	0.13	0.13	0.10	0.08	Present	Present	Grade 2, SM, 4PL; DM, aortic
33	37, M, N	205	155	88	0.09	0.12	0.14	0.09	0.08	Present	Present	DM, 3PL
34	52, M, W	240	130	54	0.08	0.12	0.16	0.12	0.12	...	...	Grade 1, SM, 3PL; DM, 3PL; PSM, apex
35†	75, F, W	190	110	92	0.07	0.08	0.10	0.09	0.10	...	...	DM, 3PL
36	42, M, W	230	120	60	0.08	0.12	0.14	0.09	0.08	...	Present	Grade 2, SM, apex; DM, 4PL
37†	66, M, N	240	125	60	0.07	0.10	0.12	0.10	0.08	...	...	Grade 3, SM, aortic; DM, aortic; PSM, apex
38†	58, F, W	210	110	60	0.07	0.10	0.13	0.07	0.06	...	...	Grade 2, SM, aortic; Grade 3, SM, apex; DM, 3PL
39	43, F, W	180	130	54	0.07	0.10	0.12	0.10	0.10	...	...	Grade 2, SM, aortic; Grade 2, SM, apex; DM, 3PL
40†	59, M, W	180	135	94	0.08	0.08	0.10	0.07	0.07	...	Present	Grade 2, SM, apex; DM, aortic
41	22, M, W	200	160	82	0.08	0.08	0.12	0.08	0.04	...	...	Grade 2, SM, aortic; DM, 3PL
42†	59, F, N	240	140	100	0.06	0.08	0.12	0.07	0.04	...	Present	Grade 2, SM, aortic; DM, 3PL
43†	57, M, W	215	140	78	0.08	0.10	0.12	0.12	0.10	Present	...	Grade 1, SM, apex; DM, 3PL
					(0.08)	(0.11)	(0.13)	(0.09)	(0.08)			

NOTE: Cases 37 and 43: dilatation of aorta visible on chest roentgenogram.
* SM = systolic murmur; DM = diastolic murmur; PSM = presystolic murmur; 3PL = third left parasternal; 4PL = fourth left parasternal.
† Digitalis therapy.
‡ Figures in parentheses represent the mean.

and patients; they were used as control subects. The recumbent blood pressure in this series of normal subjects was under 150/90 mm. Hg. These subjects were placed in a fourth group (*group IV*).

Tables I and II contain additional personal characteristics of the four groups.

METHODS AND EQUIPMENT

Conditions: The forty-three hypertensive patients and nineteen control subjects underwent phonocardiographic studies using conventional equipment (Sanborn twin-beam phonocardiograph). Seventeen of the forty-three patients with hypertension were also studied with a band-pass filter and additional amplification. All the technical studies were made in a room in the hospital which had been converted into a sound-proof chamber. The patients were usually referred to us by the members of the house staff. We determined on the ward whether the patient had a persistent hypertensive state by repeated

TABLE II
Group IV. 19 Normal Subjects

Subject	Age (yr.), Sex and Race	Blood Pressure (Recumbent) (mm. Hg)		Heart Rate (per min.)	Q-1 Interval (sec.)	First Sound (sec.)		Second Sound (sec.)	
		Systolic	Diastolic			Aortic Area	Apex	Aortic Area	Apex
1	55, M, W	140	80	71	0.05	0.14	0.16	0.05	0.06
2	43, M, W	110	80	75	0.05	0.14	0.15	0.05	0.06
3	56, M, N	120	84	94	0.06	0.07	0.13	0.07	0.06
4	69, M, N	138	80	71	0.04	0.15	0.16	0.06	0.06
5	34, M, N	125	85	66	0.06	0.14	0.15	0.05	0.04
6	44, M, W	120	80	80	0.05	0.11	0.12	0.06	0.05
7	65, M, W	140	90	92	0.04	0.14	0.15	0.05	0.05
8	50, M, W	115	85	71	0.06	0.14	0.15	0.06	0.05
9	48, M, W	144	90	79	0.05	0.18	0.22	0.05	0.06
10	42, M, W	130	95	77	0.05	0.10	0.11	0.04	0.05
11	54, M, N	130	95	98	0.07	0.11	0.14	0.06	0.05
12	39, M, W	110	85	60	0.06	0.12	0.14	0.06	0.05
13*	43, M, W	112	65	62	0.06	0.12	0.15	0.06	0.05
14	42, M, W	108	80	60	0.05	0.12	0.16	0.06	0.04
15	34, M, W	124	86	54	0.05	0.11	0.14	0.05	0.04
16	49, M, W	135	90	65	0.04	0.11	0.14	0.06	0.05
17	52, M, W	120	90	79	0.06	0.14	0.15	0.05	0.04
18	31, M, W	118	70	67	0.05	0.13	0.14	0.08	0.06
19	45, M, W	128	87	58	0.06	0.12	0.13	0.06	0.05
					(0.05)†	(0.12)	(0.15)	(0.06)	(0.05)

* Grade 2 systolic murmur at pulmonic area.
† Figures in parentheses represent the mean.

determinations of the arterial blood pressure (cuff method) after the patient had been lying in the recumbent position for several minutes. These patients were later studied by our method of phonocardiography in the sound-proof room. They were permitted freedom of activity before phonocardiography; none was sedated. The studies were made without relationship to meals. Three blood pressure determinations were made with the subject in the standing, sitting and recumbent position. The recumbent systolic and diastolic pressures are reported in the tables.

Equipment and Technic: We employed as a recording device: (1) a twin-beam phonocardiograph (Sanborn), (2) a variable band-pass filter* and (3) an amplifying stethoscope.† The technic was as follows: an electromagnetic microphone was placed over the chest of the patient and plugged into the amplifying stethoscope. A cable was connected from the output of the amplifying stethoscope to the input of the band-pass filter. The output cable of the filter was plugged into the microphone outlet (input) of the sound amplifier of the twin-beam phonocardiograph (channel A); an electrocardiogram was recorded by channel B. The low- and high-pass frequencies of the filter were set at the desired limits and the tracing was made; for example, the low and high frequency vibrations of the stethogram were cut off by selecting a frequency band of 150 to 200 c.p.s. The amplitude of the sound vibrations was controlled by the "loudness" knob of the amplifying stethoscope. In this manner we were able to regulate the sensitivity of the amplifying system so that the intensity of faint murmurs, heard on auscultation, might be satisfactorily reproduced; an audiophone was used to monitor this procedure.

Sound tracings were obtained with both the bell and diaphragm chest piece at the second right parasternal area (aortic); the second left parasternal area (pulmonic); the third, fourth and fifth left parasternal areas; the mid-precordium; and the apex. Stethoscopic records were obtained on every patient; logarithmic tracings were made on some of our patients, but the heart sound vibrations were too low in amplitude and thus were not evaluated in our study. An apex cardiogram and carotid pulse tracing were obtained on almost all the patients. The apex cardiogram was used to time the diastolic events of the heart and the carotid pulse was used to denote the time of occurrence of the second heart sound.

* Model 310AB Krohn Hite Instrument Company, Cambridge, Massachusetts.

† Model 256 Sanborn Company, Waltham, Massachusetts.

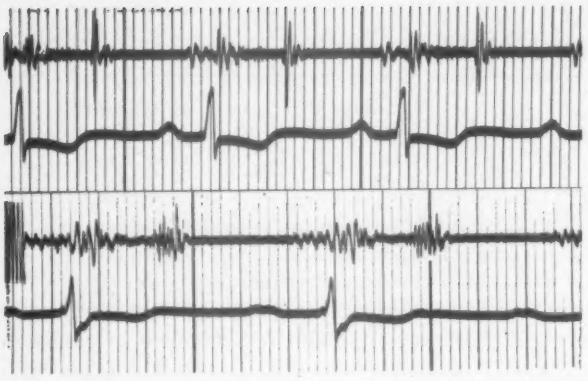


FIG. 1. Comparison of the vibrations of a fourth heart sound and a presystolic murmur. *Upper tracing*, fourth heart sound (standard phonocardiograph) recorded at apex. *Lower tracing*, presystolic murmur (standard phonocardiograph) recorded at apex.

The length of the Q-1 interval was determined in all patients. Measurements of this interval were made with the microphone placed at the apex, using lead II as a reference.

Murmurs were recorded as to intensity (system of 6 for systolic murmurs), frequency response, location in the cardiac cycle, duration and microphone position on the chest where the murmur was recorded best.

RESULTS

GROUP I

The characteristics of the patients and of the phonocardiograms are presented in Table I. In accordance with clinical experience, splitting of the first or second heart sound was not found; nor were any third heart sounds present. A fourth heart sound of low frequency and low amplitude (intensity) was present in two patients in this group. It was diphasic in configuration and occurred immediately after the P wave in the electrocardiogram. It preceded the main vibration of the first heart sound by 0.09 second. The average duration of the fourth sound was 0.04 second; it was best recorded at the apex with the bell chestpiece. An example of this sound is presented in Figure 1 (upper tracing), which was recorded in a patient in group II.

Eight of the patients in group I had systolic murmurs, which were recorded best at the apex in five patients and at the second right parasternal area in the other three (base). The apical murmurs were low in intensity (grade 1 to 2) and early systolic in time; the frequency response was in the medium range (80 to 150 c.p.s.). The basal murmur was of grade 1 intensity in two patients and grade 2 in the other; it occurred in early and middle systole and was best recorded in the frequency range of 60 to 110 c.p.s. No diastolic murmurs were recorded. All the patients in this group had a normal rate and rhythm at the time of phonocardiography. A prolonged P-R interval was not found in any of our hypertensive patients.

GROUP II

The findings in this group are presented in Table I. As in group I, no splitting of the first or second heart sound was found. Five patients had a third heart sound; this was low in amplitude, of low to medium frequency, and its duration averaged 0.06 second. The third heart sound was characterized by a monophasic or diphasic vibration that occurred 0.11 to 0.20 second after the initial main vibration of the second heart sound (average = 0.15 second). It was best recorded at the apex with the bell chestpiece. Two of the five patients with a third heart sound also had a fourth heart sound. An additional four patients had a fourth heart sound without a third heart sound being present; thus, a total of six patients had a fourth heart sound. The fourth heart sound was usually diphasic in configuration and preceded the main vibration of the first heart sound by a time interval of 0.08 to 0.13 second. The average duration of the third heart sound at the apex was 0.06 second, and the average duration of the fourth heart sound in this same area was 0.05 second. One patient had atrial fibrillation and a fourth heart sound was not present. Two patients had a fourth heart sound of greater than 0.07 second in duration; we thought that these vibrations might represent a presystolic murmur. The vibrations were low in amplitude and frequency and were not crescendo in configuration. They were recorded best with the patient lying in the recumbent position and were more readily detected with the bell than the diaphragm chestpiece.

Figure 1 (upper tracing) shows a fourth heart sound; this was recorded at the apex on the routine phonocardiogram. Figure 1 (lower tracing) represents a routine apical phonocardiogram on a patient in group II, which shows presystolic vibrations greater than 0.07 second in duration (murmur).

A mid-systolic click was present at the second and third left parasternal area on one graph. It occurred about 0.20 second after the initial main vibration of the first heart sound. Two

patients in this group had no murmurs, but a systolic murmur was present in the remaining fourteen patients. The predominant location of the systolic murmur was at the apex (nine patients); this murmur was holosystolic, of medium frequency, and the intensity varied from grade 1 to 4 (two had a grade 1 murmur; only one had a grade 4 murmur). Besides the apical murmur, two patients also had a systolic murmur at the second right parasternal area and one patient had a systolic murmur at the second left parasternal region. In addition, two patients had murmurs in the aortic area alone, and three had systolic vibrations only in the pulmonic region. These vibrations at the base of the heart were usually holosystolic in time, low in amplitude and of low to medium frequency. At the time of phonocardiography, the cardiac rate was under 60 in three patients in this group; the remaining thirteen had a heart rate between 60 and 100. One patient had atrial fibrillation; the other fifteen had sinus rhythm.

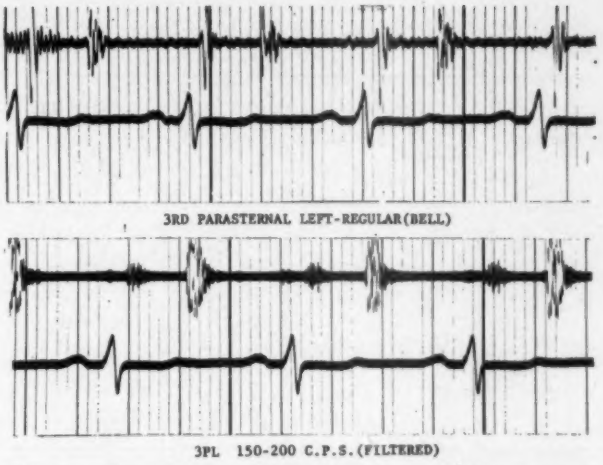


FIG. 2. Comparison of heart sounds and murmurs recorded from the third left parasternal area with a standard phonocardiograph (*upper tracing*) and a band-pass filter and further amplification (*lower tracing*). Distinct, early vibrations are not visualized in the upper non-filtered stethogram. On the lower record, vibrations of medium to high frequency are seen following a high frequency second heart sound of increased amplitude and duration. To obtain this tracing, a band of 150 to 220 c.p.s. was selected.

GROUP III

The characteristics of group III are presented in Table I. The amplitude of the second heart sound was usually greatest at the second right parasternal area. Splitting of the first or second heart sound was not present. Five patients in this group had a third heart sound; two of these patients also had a fourth heart sound of less than 0.06 second duration. An additional four patients had a fourth heart sound, making a total of six patients in this group with a fourth heart sound. The third heart sound occurred 0.16 second (average) after the initial main vibration of the second heart sound; the fourth heart sound preceded the main vibration of the first heart sound by an interval of 0.10 second (average). The average duration of both the third and fourth heart sounds was 0.05 second; they were best recorded at the apex with the bell chestpiece. Three patients had presystolic vibrations of greater than 0.07 second duration (presystolic murmur). The third and fourth heart sounds were of low frequency and low amplitude in almost all instances; on one occasion the amplitude of the third heart sound equalled that of the second heart sound.

A systolic murmur was recorded in thirteen patients in this group; the remaining two had no vibrations in systole. A systolic murmur at both the apex and the aortic area was demonstrated in two patients. Three additional patients had only an apical systolic murmur; three patients had a systolic murmur which was recorded best at the second right parasternal area; four patients had vibrations in systole which were best visualized at the third left parasternal area; and one patient had a systolic murmur with maximal intensity at the fourth left parasternal area. Systolic murmurs at the apex had an intensity of grade 1 to 3, were early and mid-systolic in time and consisted of vibrations of medium frequency. The intensity of the systolic murmur at the base was usually low (grade 1 to 2); the vibrations were of low-medium frequency and occurred, as a rule, throughout systole.

Fifteen patients in this group had conventional phonocardiograms and ten of them had special filter studies with additional amplification. All had an early basal diastolic murmur on physical examination; it should be noted that we were not able to record this murmur with the twin-beam phonocardiograph. The use of the band-pass filter combined with the amplifying stethoscope made it possible to obtain a distinct, accurate recording of this diastolic event. Figure 2 (upper tracing) represents a phonocardiogram taken with a Sanborn twin-beam phonocardiograph on a hypertensive patient who had a basal diastolic murmur; no early diastolic vibrations are seen. Figure

TABLE III
Duration of the Second Heart Sound at the Aortic Area

Group	No. of Cases	S_2 Duration (sec.): Frequency Distribution								
		0.04	0.05	0.06	0.07	0.08	0.09	0.10	0.11	0.12
I	12	...	...	4	6	2	...	...	...	...
		...	...	0.33*	0.83	1	...	...	...	...
II	16	...	...	...	4	9	3	...	...	...
		...	...	...	0.25	0.81	1	...	...	...
III	15	...	...	...	3	3	4	4	...	2
		...	...	...	0.20	0.40	0.67	0.87	...	1
IV	19	1	7	9	1	1	...	...	...	...
		0.05	0.42	0.89	0.95	1	...	...	...	...

* Represents the cumulative fraction of total number (%/100).

2 (lower tracing) demonstrates that the filter and amplifier clearly recorded the diastolic murmur on this same patient.

The basal diastolic murmur was best recorded when a frequency band of 150 to 200 c.p.s. was selected. The murmur was usually low in amplitude, evanescent and occurred immediately after a second heart sound of increased amplitude. It was confined chiefly to the protodiastolic period, was decrescendo in contour and was recorded best at the third left parasternal area and occasionally at the second right parasternal area. The murmur was more easily detected during expiratory apnea with either the bell or diaphragm chestpiece.

Two patients in this group had a cardiac rate of 54 when the phonocardiogram was recorded; the remaining rates were between 60 and 100. The rhythm in all patients was sinus.

GROUP IV

There were nineteen men in the control group. The characteristics of this group are shown in Table II. One man had a second heart sound which was slightly split at the second parasternal left area. A second man had a grade 2 early systolic murmur at the second left parasternal area. No diastolic sounds or murmurs were recorded in any subject of this group. The electrocardiograms of these persons were all with normal limits.

DURATIONS OF SOUNDS

No important differences in the duration of the first heart sound were noted. However, a steady progression of the duration of the second sound, as compared to the normal group, was observed in groups II and III with increasing degrees of pathological processes. The duration of the second sound as measured at the aortic area in the several groups is presented in Table III.

The differences between the several groups were tested with the Kolmogorov-Smirnov modification of the chi square procedure for non-parametric distributions[1]; the formula applied was:

$$x_2^2 = 4D^2\left(\frac{N_1N_2}{N_1 + N_2}\right)$$

The duration of the second sound was significantly longer in groups I, II and III than in group IV (normal). Also, the second heart sound in groups II and III was significantly longer than that in group I; the differences were not significant between groups II and III.

THE Q-1 INTERVAL

The Q-1 interval was measured in all groups and the distribution of these intervals is presented in Table IV. The differences were tested with the chi square modification used in examining the significance of differences of the second heart sound duration. The differences between groups I and II and groups I and IV were not found to be significant. Group III was found to have a statistically significant longer Q-1 interval when compared to groups I, II and IV. Differences between groups IV and II are indicated at the 5 per cent probability level.

COMMENTS

First Heart Sound: The first heart sound at the apex and the aortic area was normal in amplitude and duration in all groups studied.

TABLE IV
Length of Q-1 Interval

Group	No. of Cases	Q-1 Interval (sec.): Frequency Distribution					
		0.04	0.05	0.06	0.07	0.08	0.09
I	12	...	3	8	1	...	...
			0.25*	0.92	1	...	...
II	16	2	2	4	8	...	...
		0.13	0.25	0.50	1.00	...	...
III	15	...	...	2	4	7	2
				0.13	0.40	0.87	1
IV	19	3	8	7	1	...	...
		0.16	0.58	0.95	1	...	...

* Represents the cumulative fraction of total number (%/100).

Luisada[2] has reported that the first heart sound at the aortic area (aortic first sound) is often prolonged in some cases of hypertension. In our studies, the average duration of the first heart sound at the aortic area in the three hypertensive groups was the same as that observed in the control group (0.12 second). However, two patients in group II had a duration of the aortic first heart sound of 0.16 second and 0.17 second, respectively; these patients also had prolongation of the first sound at the apex (0.18 second in both patients). One patient in group III also had a significant increase in duration of the aortic first sound (0.15 second); in this patient the first heart sound at the apex was also increased in duration (0.16 second). Thus, we found that the aortic first sound was prolonged only in those instances when the apical first sound was long in duration.

Second Heart Sound: The second heart sound at the base is accentuated in arterial hypertension.[3] In our phonocardiographic studies at the different areas, we found that the second heart sound was longer in duration and greater in amplitude at the aortic area. It was most often composed of regular high frequency vibrations. The greatest duration of the second heart sound was seen in patients with aortic insufficiency (group III). The mean duration of the second heart sound at the apex was slightly less than that in the aortic area in both the control and hypertensive groups. We did not observe splitting of the second heart sound in any of the patients with hypertension.

Systolic Click: An early systolic click was described by Potain[4] in hypertension. McKusick et al[5]. also noted an *early* systolic click at the aortic area in a patient with severe arterial hypertension and mild dilatation and elongation of the aorta. Only one of our patients had a systolic click (in group II); this click was mid-systolic in time. This patient also had a grade 2 early systolic murmur with maximal intensity at the pulmonic region. A postero-anterior chest roentgenogram did not reveal dilatation of the ascending aorta. An early systolic ejection sound was not found in two patients who had minimal dilatation of the ascending aorta on chest roentgenogram. Although systolic clicks have been said to be due to systemic arterial hypertension (ejection dilatation of the aorta during systole), the infrequency of this finding in our study appears to indicate that this is an unlikely explanation.

Diastolic Sounds: Weitzman[6] found a fourth heart sound on phonocardiography in forty-six of 131 hypertensive patients (35 per cent). Ninety-six per cent of the forty-six patients with a fourth heart sound had left ventricular hypertrophy on electrocardiogram and chest roentgenograms; however, a significant left ventricular hypertrophy was also present in 75 per cent of the remaining group of eighty-five patients. Weitzman found that the incidence of cardiac failure was higher (23 per cent) in the group with a fourth heart sound than in that without (9 per cent); 20 per cent of the patients in whom this sound was recorded were symptom-free. Blood pressure readings in his two groups showed no significant difference. Miles[7] noted a fourth heart sound gallop on clinical examination and phonocardiography in twenty-three of one hundred hypertensive patients (23 per cent), and a third heart sound gallop in only six of one hundred patients (6 per cent),

At the time of his recording of the fourth heart sound, the average pulse rate was 90 (range = 60 to 100). When a third sound gallop was recorded, the average pulse rate was 93 (range = 75 to 106). Miles showed poor correlation between gallop rhythm and the degree of heart disease, as judged by the blood pressure, heart size, electrocardiographic abnormality and degree of cardiac failure. Our investigation generally confirms these graphic studies of Weitzman and Miles.

In our series of forty-three hypertensive patients, a *fourth heart sound* was found more often than a third heart sound. Blood pressure recording in the patients with and without a third or fourth heart sound showed no significant difference. The presence of a fourth heart sound was noted in all three groups; however, it was found more often in patients with left ventricular hypertrophy than in those without. A fourth heart sound was also noted on the graphic records of patients in all three groups who were well maintained on digitalis. Eight of the patients with a fourth heart sound had past evidence of congestive heart failure and six did not.

A *third heart sound* was found only in patients with left ventricular hypertrophy. It was noted in five patients in group II; four of them had a history of congestive failure. This sound was also noted in five patients in group III; three of them were being maintained on digitalis because of past episodes of cardiac failure. It seems from these data that a third heart sound may be recorded more often (70 per cent) than a fourth heart sound (57 per cent) in patients with congestive failure due to hypertension.

Presystolic Murmur: An apical presystolic murmur is not a rare finding in patients with hypertensive heart disease. In our study, this murmur was easily visualized on the routine phonocardiogram. Its presence was not related to an abnormality of the first heart sound; often the presystolic vibrations extended into the vibrations of the first heart sound. It is possible that the murmur may represent what Austin Flint[8] described in the past in patients with severe aortic insufficiency. In our series, two patients in group II had presystolic vibrations longer than 0.07 second in duration, which in our opinion can be classified as a distinct murmur. A presystolic murmur was found in three of the fifteen patients with aortic insufficiency (group III). This murmur was not found in patients without left ventricular hypertrophy. The presence of a presystolic murmur did not correlate with the level of the systolic or diastolic blood pressure or the height of the pulse pressure.

Although the number of patients who had a presystolic murmur is small, it seems that its existence is related to the presence of at least moderate left ventricular hypertrophy. Both patients in group II with a presystolic murmur had evidence of congestive heart failure in the past and were receiving digitalis at the time of phonocardiography. Of the three patients in group III with a presystolic murmur, two were receiving digitalis and one was not; thus a total of four of five patients with a presystolic murmur had had cardiac decompensation in the past. This indicates perhaps that this murmur is more often associated with advanced rather than early hypertensive heart disease. No mid-diastolic murmurs were recorded in any patient of the three groups.

Apical Systolic Murmur: The predominant location of a systolic murmur in hypertensive heart disease is at the apex.[9,10] In our study, systolic murmurs at the apex were found in five patients in group I, seven in group II, and five in group III. Thus, the incidence of this murmur was about the same in the three groups.

The apical systolic murmur was usually low in intensity and occurred most often in early and middle systole. Almost all apical systolic murmurs were best visualized when a band of 60 to 110 c.p.s. was selected (range = 60 to 150 c.p.s.). The presence of the murmur did not seem to be dependent on the level of the arterial pressure at the time of phonocardiography. The murmur was, as a rule, greater in intensity and longer in duration in persons with left ventricular hypertrophy. There was no essential difference in the characteristics of the murmur in those patients with and without aortic insufficiency. This murmur is believed to be due to relative mitral insufficiency.[11]

Basal Systolic Murmur: A systolic murmur at the base is not an uncommon finding in patients with hypertensive heart disease.[10] A systolic murmur at the second right parasternal area was found in three patients in group I, four in group II and five in group III. A systolic murmur with maximal intensity at the second, third or fourth left parasternal areas was not found in group I; however, it was present in four patients in group II and in five in group III.

The basal systolic murmur in patients in

group I occurred in early and middle systole and was low in intensity. In patients in groups II and III (those with left ventricular hypertrophy), the murmur at the base was holosystolic in time and also low in intensity. The basal systolic murmurs were best recorded within a frequency band of 60 to 110 c.p.s. The presence of the systolic murmur in the three groups did not seem to be associated with significant differences in the systolic, diastolic or pulse pressures at the time of the technical examination. The basal systolic murmur was generally longer in duration and greater in intensity in patients with left ventricular hypertrophy. One patient in group III with evidence of dilatation of the ascending aorta on the postero-anterior chest roentgenogram had a grade 3 systolic murmur at the base; the other patient with this x-ray finding had a grade 1 basal systolic murmur. The systolic murmur at the base in patients with hypertension is thought to be caused by turbulence near the aortic valve; Levine and Harvey[12] state that it is due to dynamic dilatation of the aorta.

Basal Diastolic Murmur: Osler[13] in 1920 first recognized an aortic diastolic murmur with hypertension and chronic nephritis. He believed that it was due to aortic insufficiency. In 1944, Hamman[14] described the murmur of aortic insufficiency in the late stages of prolonged hypertension. Aortic dilatation with actual atherosclerosis of the aortic valve was the most common pathologic feature in his study. He also reported that the peripheral vascular signs of aortic insufficiency were not present in his patients. Gager[15] claimed that aortic insufficiency was noted more often when the pulse pressure was high. In our study, we did not find the peripheral vascular manifestations of aortic insufficiency in any of the fifteen patients. Hamman mentioned that he found the murmur in patients with prolonged hypertension. We observed that some of our patients with a basal diastolic murmur had had hypertension for only two years.

In 1956, Luisrda et al.[16] described a technic of selective phonocardiography in which they used a variable band-pass filter and a twin-beam phonocardiograph. We modified this system by adding another amplifier (amplifying stethoscope); thus, we found we were able to increase the sensitivity of our recording apparatus and to demonstrate a much clearer registration of vibrations of low amplitude in a selected frequency band. With this technic, we were able to record the faint basal diastolic murmur in nine of the ten patients in whom it was heard. We believe that this murmur represents insufficiency of the aortic valve, since its point of maximal intensity occurs over the aortic valve and it immediately follows an accentuated second heart sound. This murmur had a medium to high frequency, and only by eliminating the low frequency vibrations and some of the medium frequency vibrations were we able to achieve a suitable recording of the murmur. The diastolic vibrations were demonstrated over a wide frequency range, but they were visualized most clearly when a frequency band of 150 to 200 c.p.s. was selected. We were not able to record this murmur on the routine phonocardiogram; nor were these vibrations present when a low frequency band was selected (20 to 80 c.p.s.).

Ten of the fifteen patients who had the basal diastolic murmur (group III) had moderate to marked left heart enlargement on physical examination and chest roentgenogram. This degree of hypertrophy was also found in ten of the sixteen hypertensive patients without aortic insufficiency (group II). Two of the patients in group III had x-ray evidence of dilatation of the ascending aorta. None of the patients without aortic insufficiency had this finding. The presence of the diastolic murmur did not seem to bear any relationship to the level of the systolic or diastolic blood pressure at the time of phonocardiography. These vibrations were not seen in some patients with an abnormally high pulse pressure. The arterial pressures in group III were similar to those in group II, but were generally higher than those in group I.

Q-1 Interval: The Q-1 interval was prolonged in the hypertensive patients as compared to the control group. The average duration of the Q-1 interval in our normal subjects was 0.05 second; the mean in the hypertensive groups was 0.07 second. The longest Q-1 intervals were found in group III; the mean in these patients was 0.08 second. Our findings are comparable to those of Leonard et al.[17] who reported a prolonged Q-1 interval in a study of hypertensive patients. The significance of a prolonged Q-1 interval in hypertension is open to some question, since a number of sources of error may be present. A wide QRS complex in lead II usually will be associated with a prolongation of the Q-1 interval. Also, a Q-1 interval may be 0.02 to 0.04 second longer

when it is measured nearer to the xiphoid area than the apex. The reason for this prolongation of the Q-1 interval in hypertension is unknown.

Summary

Forty-three patients with hypertension were studied by an improved method of phonocardiography. On graphic analysis, the first heart sound at the apex and aortic area was generally normal in amplitude and duration. The second heart sound at the aortic area was increased in amplitude and duration in almost all instances. It was usually composed of regular high frequency vibrations. Third and fourth heart sounds of low frequency and low amplitude were found quite often. A third heart sound was noted only in the presence of left ventricular hypertrophy.

An apical presystolic murmur of low frequency and low amplitude was recorded in five patients. Aortic and apical systolic murmurs were noted often; these murmurs were usually low in intensity and of low to medium frequency.

A basal diastolic murmur was recorded in nine of ten patients in whom the murmur was heard clinically. We believe that it suggests insufficiency of the aortic valve. The diastolic vibrations were low in amplitude and more readily detected when a frequency band of 150 to 200 c.p.s. was selected. They immediately followed the second heart sound and were best visualized at the third left parasternal area. The presence of the murmur did not seem to be related to the level of the systolic, diastolic or pulse pressures at the time of the technical procedure. It was found only in patients with left ventricular hypertrophy.

The Q-1 interval was prolonged, particularly in the group with aortic insufficiency.

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Reviews

Evaluation of Enzyme Tests in the Diagnosis of Heart Disease*

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ENZYME tests, which are undergoing extensive investigation, are becoming increasingly useful in the diagnosis of heart disease. Because of the growing literature on the subject since the first review,[1] a further evaluation has become necessary.

EXPERIMENTAL ASPECTS

The clinical problem of distinguishing myocardial infarction from coronary insufficiency by measuring enzyme changes is still not solved. Experimentally, however, the evidence remains clear-cut.

Further experiments on dogs by Ruegsegger et al.[2] showed invariable elevation of serum glutamic oxalacetic transaminase (SGO-T), serum glutamic pyruvic transaminase (SGP-T) and serum lactic dehydrogenase (SLD) in decreasing order, following experimental myocardial infarction. Reversible myocardial ischemia accompanied by electrocardiographic changes did not cause elevation. Therefore, the experience to date indicates that cellular death is necessary for enzyme release following obstruction to coronary flow.

Foldi et al.[3] produced significant elevation of SGO-T in dogs after experimental paracardial lymphatic obstruction, with accompanying histologic changes in the myocardium. No experience in man has yet been reported in which obstruction of paracardial lymphatics has confused the diagnosis of myocardial infarction.

Maling and Highman[4] induced prolonged states of ventricular hypersensitivity in dogs similar to that seen in myocardial ischemia by infusions of large amounts of catecholamines. The resulting myocardial irritability caused ventricular tachycardia, lasting for two to four days, which was associated with fatty changes in the myocardium and elevations of SGO-T, SGP-T and SLD. These elevations could be blocked by the administration of Dibenzyline.® Thus, experimental evidence is offered for the clinical observation that prolonged rapid tachycardia can cause enzyme elevations.[2,5]

CORRELATION OF CLINICAL MYOCARDIAL INFARCTION WITH SGO-T

Whether or not the serum glutamic oxalacetic transaminase test is reliable can only be determined by a summation of the experiences of many observers. In the final analysis, summation will also determine clinical usefulness and dependability of the test. While clinically "proved" cases are not really proved unless death affords autopsy confirmation, the considered opinion of able clinicians, based on the entire clinical course of the patient, in conjunction with diagnostic supportive electrocardiographic and other laboratory data, is highly significant.

Therefore, although not infallible, such diagnoses have been accepted in this evaluation and are listed in Table 1. The only exceptions are the same as those in the first report,[1] in which the natural time curve of the rise and fall in SGO-T was not followed. It is still necessary to

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TABLE I
Clinical Correlation of Acute Myocardial Infarction with SGO-T

Authors	No. of Proved Cases	Elevated SGO-T	Normal SGO-T
Hanson and Laursen[14]	87	84	3*
Dewar et al.[49]	34	31	3
Bruce et al.[48]	21	20	1
Keele et al.[10]	75	73	2
Paget et al.[50]	13	13	0
Zapfe[51]	75	71	4
Bang et al.[15]	31	31	0
Sampson[26]	23	20	3†
Freeman et al.[24]	60	60	0
Lewis et al.[29]	18	18	0‡
Total	437	421	13

* Of eighty-nine cases, two were deleted because tests were made one to two weeks after onset.

† Actually, all three patients had borderline elevations but are counted as "normals."

‡ Two of twenty cases were omitted because tests were made four and six days after onset of pain.

TABLE II
Myocardial Infarction Proved at Autopsy

Authors	Elevated SGO-T	Normal SGO-T
Hanson and Laursen[14]	21	0
Linde and Wising[52]	13	0
McHardy and Statler[53]	4	2*
Hanson and Biorck[8]	7†	0
Dewar et al.[49]	3	0
Bruce et al.[48]	4	1‡
Keele et al.[10]	5	0
Total	57	3
Previous report[1]	62	1
Grand total	119	4

* Reported as "borderline."

† One negative case, but infarct one week old.

‡ Author stated, "taken at time of infarct."

emphasize that enzyme sampling must be begun twelve to twenty-four hours after the onset of infarction and continued at daily intervals until the values have returned to normal. Random sampling may not reflect the period of SGO-T elevation and will not eliminate technical errors.

In the 437 most recently reported cases, 421 of the subjects showed elevations of SGO-T, giving a correlation of 96.3 per cent. This compares favorably with the 1,255 previously reported cases[1] in which the correlation was 96.9 per cent. Thus, in more than 96 per cent of 1,692 cases, SGO-T levels correlated with the clinical impression of myocardial infarction. This figure represents the combined opinion of thirty-six independent reports.

Autopsy Correlation of Myocardial Infarction with SGO-T

Of those cases terminating in death, in which autopsy was obtained, SGO-T was elevated in fifty-seven of the sixty cases reported (Table II). In two instances, SGO-T was "borderline." In the one negative case, SGO-T was taken "at the time of infarct." These figures are similar to the sixty-two positive correlations of the sixty-three cases previously reported.[1] Therefore, in 123 patients, whose hearts at autopsy showed recent infarction, SGO-T was significantly elevated in 119, not to mention two patients with borderline values, and one in whom SGO-T was measured before a rise could be expected. Thus, there is a correlation of approximately 97 per cent.

Often, enzyme tests are not necessary for the diagnosis of myocardial infarction. Before they came into use, the diagnostic accuracy was estimated at 58[6] to 82[7] per cent. Therefore, if the tests are to have lasting value, they must prove reliable when clinical and electrocardiographic data are insufficient.

Some evidence is again supplied by the data on the seventeen autopsied subjects listed in Table III. These were subjects in whom infarction was proved by necropsy, but in whom clinical and electrocardiographic evidence for myocardial infarction was absent or inconclusive. Of the seventeen subjects, sixteen showed significant elevations, one was borderline and none was normal. With the two cases previously reported,[1] we now have eighteen of nineteen subjects in whom autopsy proved SGO-T studies to be reliable when clinical and electrocardiographic evidence failed to make the diagnosis.

It can also be asked whether SGO-T has been shown to have superior diagnostic value when the clinical picture and the electrocardiogram indicate infarction, but when the enzyme curve is *flat* or *negative*. In four autopsied subjects, reported on by Hanson and Biorck,[8] two were proved to have pericarditis, one had

TABLE III

Infarction Proved at Autopsy in Seventeen Patients with Negative Clinical and/or Electrocardiographic Evidence of Myocardial Infarction

Authors	Elevated SGO-T	Borderline SGO-T
Hanson and Biorck[8]	3	0
Chinsky et al.[5]	7	1
Kessler and Phelps[64]	1	0
Ostrow et al.[19]	2	0
Hanson and Laursen[14]	3*	0
Total	16	1

* One with only old infarction.

persistent tachycardia and one had cerebral, pulmonary and renal, but not myocardial, infarctions. In the previous review,[1] two subjects with clinical and electrocardiographic evidence of infarction, but negative SGO-T values, showed no infarction at autopsy.

Ratner and Sacks[9] also reported negative SGO-T rises in four subjects in whom the diagnosis of myocardial infarction was made clinically and by electrocardiography, but in only one subject was infarction proved at necropsy. Although each of these subjects had only single blood sampling, the blood was drawn from one to three days after clinical infarction. Thus, of the ten cases in which autopsy reports were available, SGO-T negative evidence was reliable nine of ten times.

On the other hand, in three cases reported by Keele et al.,[10] in which there was suspicion of myocardial infarction, suggestive electrocardiographic changes, chest pain and *elevated* SGO-T, necropsy showed the first patient to have cor pulmonale with no myocardial infarction; the second, mediastinal tumor with metastases to liver and myocardium; and the third, bronchitis with electrocardiographic evidence of right ventricular strain. Their peak SGO-T levels were 80, 100 and 60 units, respectively. Therefore, an elevation of SGO-T with a clinical and even an electrocardiographic picture of myocardial infarction may be confused with such conditions as pericarditis, severe tachycardia and acute cor pulmonale.

Disease States Confusing Diagnosis of Myocardial Infarction

In making a firm diagnosis of acute myocardial infarction, there are several confusing disease states that must be eliminated. Nearly all of these can cause chest pain, fever, leukocytosis, increase of the sedimentation rate, alteration of the electrocardiogram and elevation of serum enzymes.

Pericarditis: In the last two years, only seven additional cases of pericarditis correlated with SGO-T changes have been reported. In three cases of non-specific pericarditis,[11] SGO-T was elevated in two, with peak levels to 116 to 165 units. Keele et al.[10] reported one case in which the peak level was 124 units, and one autopsy case of hemorrhagic pericarditis in which elevation was present.

Including those previously reviewed,[1] there are now forty-eight reported cases of acute pericarditis; SGO-T elevations were found in eight. In the cases previously reviewed, the highest peak values were 75 and 165 units. From animal experiments,[12] it was found that SGO-T elevation occurred only when the pericarditis was severe enough to cause subepicardial myocardial infarction. So far, there are no human cases in which similar autopsy studies have been made, but it is to be expected that in such cases subepicardial infarction will be present.

It can still be stated that a negative SGO-T curve is strong evidence against infarction when pericarditis confuses the picture. If severe pericarditis does elevate SGO-T, the peak values are usually low; nevertheless, enzyme tests cannot make the differential diagnosis in such instances which, fortunately, are rare.

Pulmonary Infarction: As has been pointed out,[1,13] pulmonary infarction with elevated SGO-T curves can usually be distinguished from myocardial infarction because the SGO-T rises are late (third or fourth day). The pulmonary infarcts are usually large enough to be seen on the roentgenogram (because lung tissue is poor in SGO-T) and a rise in serum bilirubin usually parallels the rise in SGO-T. In forty-nine cases previously reviewed,[1] SGO-T was elevated in twelve, the highest peak value being 85 units. Since then, Hanson,[14] Bang,[15] Keele,[10] Goldstein[16] and their co-workers have added eleven more cases, with elevations in four. In a case reported by Keele,[10] the peak elevation was 140 units. Thus, of sixty cases, sixteen subjects showed SGO-T elevations.

Dissecting Aneurysm of the Thoracic Aorta: Tredway and Kemble[17] reported three cases of dissecting aneurysm of the thoracic aorta with SGO-T determinations. Two of the three

TABLE IV
Serum Lactic Dehydrogenase Levels in Clinically Proved Myocardial Infarction

Authors	No. of Cases	Elevated	Normal
Hanson and Biorck[8]	47	38	9
Wroblewski et al.[55]	13	13	0
Wacker et al.[56]	22	22	0
Bang et al.[15]	31	26	5
Freeman et al.[24]	60	35	25
Wilson et al.[57]	23	23	0
Lewis et al.[29]	20	20	0
Snodgrass et al.[25]	66	66	0
Total	282	243 (86%)	39 (14%)

subjects had elevations of SGO-T activity and associated pericardial tamponade. Various explanations for the rise in SGO-T to peaks of 115 and 135, respectively, were offered: hemolysis of dissecting blood, absorption of blood from the pericardial sac and damage to heart muscle. No final conclusion was reached, except that dissecting aneurysm could elevate SGO-T in the absence of myocardial infarction. White[18] reported elevation of lactic acid dehydrogenase (LDH) in a ruptured aortic aneurysm.

Congestive Heart Failure: In previous studies,[1,19] normal levels of SGO-T have been found in congestive failure in the absence of myocardial infarction or liver disease. Shields and Shannon,[20] however, have described three patients with acute congestive failure and severe hepatic congestion in whom peak values of SGO-T were found to range from 700 to 3,000 units, averaging 1,510 units. Only one patient was in shock. At autopsy central lobular liver cell necrosis was found in two of them. In nine patients with shock and congestive failure complicating myocardial infarction, SGO-T ranged from 430 to 2,050; six of these patients died. Further work is needed to determine whether or not severe congestive failure alone can occasionally elevate SGO-T.

Pancreatitis: Foulk and Fleisher[21] reported increased SGO-T activity in twenty-two of thirty-two patients with acute pancreatitis. Correlation of the values for serum amylase or lipase, or both, with transaminase activity, was not demonstrated; nor was there any correlation with the pancreatic damage shown surgically or at necropsy.

No recent work has added much to the previous studies in this field.[1] Since both pancreatitis and myocardial infarction can cause substernal and epigastric pain, enzyme elevations and electrocardiographic changes,[22] differential diagnosis may, at times, prove difficult. In these instances, elevation of amylase in the blood and urine is invaluable evidence of pancreatitis, since myocardial infarction does not elevate amylase. However, the administration of opiates (codeine, morphine and meperidine) will elevate amylase,[23] just as it elevates SGO-T when given for relief of pain in acute cholecystitis.[1] It should be remembered, therefore, that serum and urine samples must be obtained before the administration of opiates.

USE OF OTHER ENZYME TESTS

Much interest has been shown in determining the comparative usefulness of various other enzymes found in heart muscle.

LACTIC ACID DEHYDROGENASE

Several authors have considered SLD equal or superior to SGO-T in the diagnosis of myocardial infarction.[24,18] In a recent report by Snodgrass et al.,[25] a rise in LDH occurred in all twenty-eight cases of myocardial infarction proved at autopsy; whereas there was no elevation when the autopsy evidence showed no infarction, even though a positive diagnosis had been made on clinical grounds. LDH was reported elevated between the second and tenth day after onset in sixty-six electrocardiographically proved cases. Furthermore, the authors claim that if LDH remains negative in suspected infarction, "the diagnosis can be ruled out with certainty."

Other authors, however, do not agree with these findings. The available reports correlating SLD values with clinically proved cases of myocardial infarction are listed in Table IV. Of 282 cases, 243 subjects exhibited positive elevations and thirty-nine exhibited no elevations: a correlation of 86 per cent. Hanson and Biorck[8] found eleven elevations in eleven cases of infarction proved by necropsy. They stated, however, that SLD appeared "to be less specific than SGO-T and more likely to render false positives." Nearly all authors agree that SLD is a good enzyme test of myocardial infarction, particularly since elevated activity following infarction may sometimes last as long as two weeks. It is thus most

valuable when used several days following the onset of infarction, after the peak of SGO-T has passed.

SLD has several disadvantages when compared to SGO-T. The normal values are variable depending upon the method used.[26] Van Rymenant and Tagnon[27] place the normal range from 200 to 600 units per ml. of serum, depending upon the reaction: lactic acid + DPN $\rightleftarrows$ pyruvic acid + DPNH. If the amount of reduced diphosphopyridine nucleotide formed is measured, normal values fall below 270 μM per 100 ml. of serum. SLD is less sensitive than SGO-T, since its activity in heart muscle is 3,000 times greater than serum, as compared to SGO-T, the activity of which is 5,000 to 10,000 times greater in heart muscle than in serum.

Wieme,[28] utilizing the electrophoretic technic, found that LDH moved in the electrical fields at different rates according to the type of tissue involved. He found four fractions of different electrophoretic mobilities and, in serums of patients with myocardial infarction, the rapid fractions were clearly augmented; while in serums of patients with hepatic disease, the slow fractions were predominant. Finally, SLD is less specific than SGO-T. Lewis et al.[29] found SLD elevated in twenty of twenty patients with proved myocardial infarction. But, three of nine who were diagnosed as having coronary insufficiency and two of six as having angina had significant elevations. Elevated serum levels are found in 25 to 50 per cent of patients with malignant tumors, with dissemination particularly to the liver and heart.[30] LDH is elevated in acute leukemias and in chronic myelogenous leukemia, malignant lymphoma, sickle cell anemia and pernicious anemia, as well as in sprue, hepatitis, diabetic acidosis, shock states[31] and renal diseases. West and Zimmerman[32] have reported elevations of SLD in forty-three of seventy-one patients with renal disease; whereas SGO-T was elevated in only six of sixty-three patients with renal disease, four of whom had coincidental hepatic disease. This relative lack of specificity appears to be an important disadvantage.

SERUM ALDOLASE

Another important enzyme released from injured cells is aldolase, a glycolytic enzyme. Volk et al.[33] demonstrated increased levels of serum aldolase in dogs after acute myocardial infarction. Chazov and Savina[34] found aldolase increased in dogs with experimental infarction, with activities increased to four or five times that of the control animals. The concentration of the enzyme begins to increase five to six hours after ligature of the coronary artery, and reaches its maximum within the first two days. By the fifteenth day, the aldolase activity returns to normal.

Petersen[35] determined the aldolase activity in serum from fifty healthy human subjects and 144 patients hospitalized with suspected myocardial infarction. He found the normal range of serum aldolase activity to be from 3 to 10 units. Sixty-one of the latter group had definite electrocardiographic evidence of infarction and all showed aldolase elevations. In fifty-six miscellaneous conditions without evidence of infarction, there was no rise in aldolase. In five cases of infarction, five to ten days old, all five patients showed slight elevations. In the remaining twenty-two patients with electrocardiographic patterns of infarction but with elevated aldolase values, however, no diagnosis was established except in two patients in whom autopsy showed recent infarcts. Aldolase was also slightly elevated in three patients with pericarditis, in eleven of twelve patients with pulmonary infarction and in one patient with cholecystitis after administration of opiates.

Hanson and Biorck[8] also found aldolase values to parallel those of SGO-T after myocardial infarction. The aldolase test, however, lacks the intensive investigation that is behind SGO-T. Moreover, exercise has been found to alter its level in the rat[36] and, since the red cell is very rich in aldolase, slight hemolysis produces a large error.[37, 38]

OTHER SERUM TESTS

Serum Glutamic Pyruvic Transaminase (SGP-T): Lewis et al.[29] found SGP-T elevated in seven of eighteen patients with electrocardiographic evidence of infarction. Furthermore, elevations were found in some patients with coronary insufficiency and angina. It is generally agreed that SGP-T is much more valuable in the diagnosis of liver disease, when it usually exceeds SGO-T elevations.

C-Reactive Protein: Kroop and Shackman[39] found C-reactive protein (CRP) to be more sensitive than SGO-T. Since it caused elevations in too many other conditions, however, it was judged to be unsatisfactory for specific use in the diagnosis of myocardial infarction. CRP, like the sedimentation rate and

TABLE V
Surgery and SGO-T

Authors	No. of Cases	No. Elevations	Peak (units)	Days Elevated	Remarks
Lawrence and Shulkins[58]	12	5	40		
Lawrence and Shulkins[58]	6	1	49		Cholecystectomy
Craver et al.[42]	20		200	2	Peak 4 hours post-operation
Craver et al.[42]	13		70	2	
Weisberg and Sampson[43]	13*	1	144	2	Liver damage
Weisberg and Sampson[43]	4†	2	78–90	8 (infarct)	Pneumonectomy: 78 units Infarct: 90 units
Weisberg and Sampson[43]	4‡	0	0		

* Laparotomy.
† Major surgery.
‡ Minor surgery.

blood fibrinogen, is also increased by congestive failure, neoplastic, collagen and inflammatory diseases.

C-reactive protein level was determined by Carbajal et al.[40] in thirty-eight persons with coronary artery disease. Nineteen had occlusion with myocardial necrosis, sixteen had coronary insufficiency without necrosis and three had infarction and cicatrization. The test result for CRP was positive only in the group with myocardial infarction. If this observation is substantiated, the differential diagnosis of myocardial infarction from coronary insufficiency may be facilitated by a negative CRP reaction.

Effect of Anticoagulants on SGO-T and SGP-T

Wroblewski and Manso[41] have observed that administration of certain anticoagulants, including bishydroxycoumarin (Dicumarol®) and ethyl biscoumacetate (Tromexan®), may be associated with increased SGO-T and SGP-T activity. This effect was seen in two patients with liver disorders. One had congestive hepatomegaly and the other, Laennec's cirrhosis. Both patients also had incurred myocardial infarction. After the administration of single doses of 200 mg. Dicumarol, rises in the two enzyme activities were noted. In the first case the SGP-T and SGO-T activities rose to peak values of 60 and 52 units, respectively, and then returned to the normal range within several days; in the second case, the SGO-T and SGP-T increased to levels greater than SGP-T prior to the administration of the anticoagulant. With the administration of Dicumarol, both the SGO-T and SGP-T activities rose, the latter to greater activity than the former. Increased SGO-T and SGP-T activity also increased in a patient given Dicumarol for thrombophlebitis during the incubation period of homologous serum hepatitis. Since no other reports of this kind have appeared, further work is greatly needed.

Surgery and SGO-T

The diagnosis of myocardial infarction complicating surgery, when the history is obscured by anesthesia or pain after surgery and when the electrocardiographic findings are inconclusive, is often difficult. It is known that damage to skeletal and heart muscle can elevate SGO-T. Table v lists the cases so far studied after surgery.

The peak values and time curve of SGO-T elevation after surgery often differ sufficiently from those of myocardial infarction to allow separation. Peak values from surgery alone rarely approach those seen in myocardial infarction, often are not elevated at all and, in most cases, reach peaks in four hours postoperatively, a time when postinfarction patients show little or no elevation. Even when occasional high values are reached, the return to normal levels is rapid; usually one or two days, as compared to five to seven days for most instances of myocardial infarction.[42] These distinctions make differential diagnosis much easier than previously believed.[43] LaDue,[44] however, has found massive surgery to cause significant and prolonged elevations.

After intracardiac surgery, Snyder et al.[45] have found an increase in the SGO-T activity, and suggest that the development of hepatic changes during perfusion was the major source of increased SGO-T values.

Prognosis

Since the original work with animals, indicating that the rise of SGO-T was roughly proportional to the size of the infarct,[46] it has been hoped that the peak level of SGO-T would offer a solid basis for prognosis. We have shown previously that a value over 300 units has indicated a much poorer prognosis. LaDue[47] has reported a poor outlook in patients with SGO-T levels greater than 350. Sampson[26] reported poor results in patients having levels of about 200, although some patients with higher values survived. Bruce et al.[48] found, in four of seven fatal cases, that the levels were greater than 350.

Hanson and Laursen[14] found a direct correlation, with the mortality rising to 50 per cent in those having high levels. Keele et al.[10] found that eight of nine patients with values greater than 350 died, whereas only three of fifty-seven with values below 100 units died. Shields and Shannon[20] observed only one death in nine patients having average SGO-T levels of 482 (range: 400 to 675), but six deaths in nine cases in which SGO-T levels averaged 886 (range: 430 to 2,052). Two patients with values of 3,000 and 830 died. All nine patients had severe congestive heart failure with hepatic central lobular necrosis. Only Dewar et al.[49] found no correlation. On the other hand, death has occurred with minimal infarction and low SGO-T rises.

Thus, there is no absolute relation between the SGO-T level and the prognosis, but the weight of evidence shows a significant correlation. The greater the injury, the higher the SGO-T and the worse the prognosis. Generally, in patients with peak elevations of less than 100 units, the prognosis is good; whereas in patients with a peak value greater than 350 units produced by myocardial infarction alone and not by some associated disorder, such as liver disease, the prognosis is poor. These levels, while arbitrary, are still of great aid to the physician in forming an optimistic or guarded outlook.

Summary

1. The recent literature on enzyme tests is reviewed and compared with the results of a previous evaluation.

2. It is found that, experimentally, SGO-T is elevated only when actual myocardial infarction has occurred.

3. In a correlation of SGO-T elevation with 1,692 clinically proved cases of myocardial infarction, the agreement was 96 per cent.

4. In a correlation of SGO-T elevation with 123 cases of myocardial infarction, proved at necropsy, the agreement was 97 per cent.

5. In eighteen of nineteen cases proved at necropsy, in which clinical and electrocardiographic evidence for myocardial infarction was indecisive, SGO-T diagnosis (elevation) was reliable.

6. In the ten autopsy cases so far available, in which SGO-T was not elevated in the face of clinical and electrocardiographic evidence of myocardial infarction, SGO-T diagnosis agreed with autopsy diagnosis in nine.

7. The association of a clinical and electrocardiographic picture of myocardial infarction with SGO-T elevation may be simulated by severe pericarditis (eight of forty-eight cases), severe pulmonary infarction (sixteen of sixty cases), dissecting aneurysm (two of three cases), acute pancreatitis, acute cholecystitis after administration of opiates, severe prolonged tachycardia and, possibly, acute cor pulmonale.

8. Elevations of SGO-T, accompanying surgical procedures, may be distinguished from those occurring with complicating myocardial infarction by the early peak (four hours) and the quick return to normal (one to two days) in the uncomplicated cases.

9. SGO-T has proved valuable in prognosis, since peak values below 100 units have been associated, in general, with a low mortality, while values over 350 units have been associated with a high mortality.

10. Other enzyme tests, particularly SLD and aldolase, are useful in the diagnosis of myocardial infarction; but their accuracy, sensitivity and specificity have not been found equal to SGO-T. Therefore, the SGO-T determination still remains the most valuable enzyme test for the diagnosis of myocardial infarction.

Acknowledgment

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Coarctation of the Abdominal Aorta

Review of Twenty-Seven Cases*

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COARCTATION of the aorta is usually located in the aortic isthmus, distal or proximal to the ligamentum arteriosum or ductus arteriosus. In a small number of cases the aortic arch, the lower thoracic aorta or the abdominal aorta is involved. The diagnosis of atypically located coarctations is important when surgical treatment of coarctation is considered. This concerns cases of coarctation of the abdominal aorta in particular, because the patient may be subjected to unnecessary thoracotomy if the abdominal localization of coarctation remains unnoticed.

Clinical features of coarctation of the abdominal aorta may sometimes be confusing. However, the diagnosis is not difficult if some special features indicating the abdominal localization of coarctation are kept in mind. From the surgical point of view, coarctation of the abdominal aorta presents special difficulties. Recent progress in vascular surgery has, however, made surgical treatment possible in selected cases.

A report is presented of a case of coarctation of the abdominal aorta. Essential features of twenty-six cases recorded in the literature are briefly summarized.

CASE REPORT

A twenty year old unmarried woman was admitted to the Hospital of the Wihuri Research Institute on January 2, 1958, because of unexplained hypertension. The only subjective complaints of the patient were fatigue, numbness, and cramp-like pains in the hips and legs related to walking. These symptoms had been present for five years.

The blood pressure had been measured for the first time in February 1957 and was 150/100 mm. Hg at that time. In July 1957 blood pressure was 230/130 mm. Hg and the patient was hospitalized. Rauwolfia alkaloids and ganglionic blocking agents were administered, but the blood pressure remained high (210–240/105–130 mm. Hg).

Physical examination on admission revealed a well developed woman. The apex beat of the heart was felt in the usual location and was of normal quality. A short, low-pitched grade 2 systolic murmur was best heard at the second left interspace. A strong pulsation of the abdominal aorta was felt in the epigastrium, but it disappeared below the level of the umbilicus. The pulsation of both femoral arteries was very faint, whereas the peripheral arterial pulsations were distinctly felt in both lower extremities. No arterial pulsations could be palpated in the intercostal spaces or on the abdomen. A continuous murmur, consisting of a grade 3 systolic ejection murmur which continued as a fainter decrescendo diastolic murmur, could be heard in the left region of the epigastrium. The systolic part of the murmur was transmitted to the femoral arteries and was also heard in the back from the level of the first lumbar vertebra to the sacrum. No murmurs could be heard over the lower intercostal spaces. The blood pressure in both arms was 240/140 mm. Hg and the systolic blood pressure in both legs was 160 mm. Hg. The diastolic blood pressure could not be measured. On ophthalmoscopic examination the retinal arteries and the fundi appeared normal.

Laboratory findings included a normal blood count, sedimentation rate and urinalysis. Blood nonprotein nitrogen content was 25 mg. per 100 cc. and the creatinine content was 0.81 mg. per 100 cc. Endogeneous creatinine clearance was 105 cc. per minute per 1.73 M^2 of body surface area.

Graphic Tracings: The electrocardiogram was suggestive of left atrial and left ventricular hypertrophy. Phonocardiograms from the left epigastrium were recorded simultaneously with indirect tracings of carotid and femoral pulses (Fig. 1) and were compared with apical phonocardiograms. Recording of the femoral pulse was difficult even with a sensitive infratone pulse microphone. The onset of the femoral pulse occurred 0.10 second after the onset of the carotid pulse and the peak of the femoral pulse 0.12 second after the peak of the carotid pulse. Phono-

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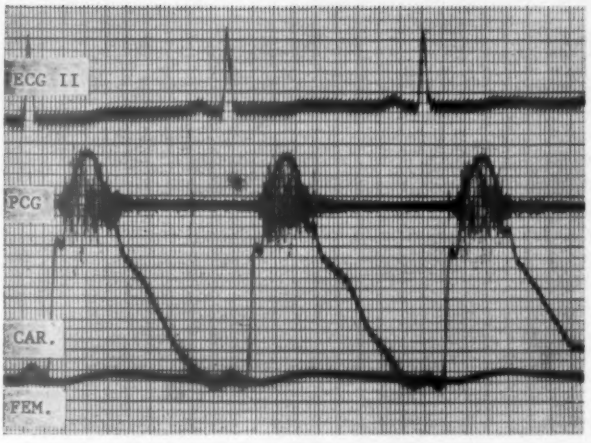


FIG. 1. *Phonocardiogram from the left epigastrium* (200 c.p.s., gain $^1/_{10}$), with electrocardiographic lead II and indirect carotid and femoral tracings, reveals a continuous murmur consisting of a diamond-shaped systolic murmur which continues as a faint decrescendo diastolic murmur.

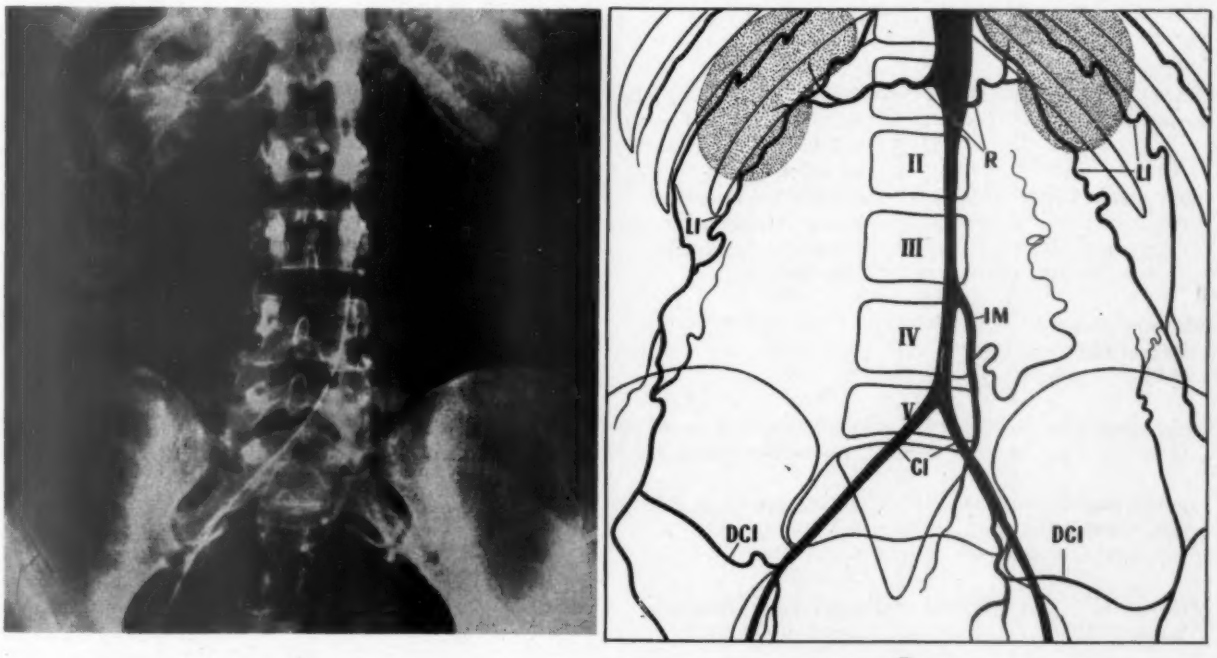
cardiograms from the left epigastrium revealed a diamond-shaped murmur which began 0.14 second after the first heart sound, between the upstrokes of the carotid and femoral pulses, and diminished in amplitude 0.7 second after the aortic component of the second sound. The murmur then continued as a decrescendo murmur of small amplitude.

Roentgenographic examination of the chest revealed no definite cardiac enlargement (total heart volume 680 cc. = 430 cc. per M^2 of body surface area). The left atrium seemed to be slightly enlarged, but otherwise the shape of the heart was normal. There was no notching of the ribs.

Pharmacologic Tests: Rapid intravenous injection of 400 mg. of tetraethylammonium chloride with the patient supine produced a decrease in blood pressure from 230/130 to 150/100 mm. Hg during three minutes; in ten minutes the blood pressure rose again to 200/130 mm. Hg. Intravenous injection of 5 mg. of pentholamine methansulphonate caused during three minutes a decrease in blood pressure from 230/110 to 195/100 mm. Hg; in ten minutes the blood pressure rose to 215/115 mm. Hg.

Excretory urograms showed that the right kidney was somewhat smaller than the left. Excretion of the left kidney was normal; that of the right kidney was slightly delayed. Both ureters and the bladder were catheterized and simultaneous urine samples were collected from both kidneys according to the technic described by Howard et al.[1] The urine minute volumes excreted by each kidney were almost identical and there was no significant difference in the sodium and creatinine content of the urine from either kidney.

Aortography was performed by injecting the contrast substance through a catheter introduced from the right femoral artery into the upper abdominal aorta (Fig. 2). Serial films showed that the aorta was of



A B

FIG. 2. A, *retrograde abdominal aortogram* with catheter introduced through the right femoral artery. B, *schematic reproduction* of the essential findings revealed by aortography. CI = common iliac artery, DCI = deep circumflex iliac artery, LI = lower intercostal arteries, R = renal arteries. The aorta becomes narrow between the first and second lumbar vertebrae and then remains hypoplastic down to the bifurcation. The common iliac arteries are hypoplastic. Numerous collaterals originate from the enlarged and tortuous intercostal arteries and also from the visceral arteries.

TABLE
Essential Features of Twenty-Seven Cases of Coarctation

Author	Age (yr.) and Sex	Symptoms	Blood Pressure (mm. Hg)		Murmurs over the Abdomen and Back
			Upper Limbs	Lower Limbs	
Quain,[2] 1847	50, M	Epigastric pains on exertion, (1 yr.)	...	...	
Power,[36] 1861	17, M	Palpitations; epileptiform attacks; "fever"	...	...	
Maycock,[8] 1937	18, F	Palpitations, dyspnea, precordial pains (5 yr); headache; pains in the back (2 yr.); claudication (8 mo.)	200/89	130/110	Systolic, in the left epigastrium, posteriorly between the left scapula and 3rd lumbar vertebra
Steele,[37] 1941	46, F	Headache; vertigo (17 yr.); signs of cardiac failure (2 yr.)	210–260/ 120–180	100–120/ 96–100	...
Bahnson, et al.,[22] 1949	35, F	Claudication (6 yr.); headache; vertigo; dyspnea; edema of the legs (1 yr.); attacks of precordial pains	195–260/ 100/130	Not measurable	Systolic, in the left epigastrium, posteriorly over 10th dorsal vertebra
Kondo et al.,[16] 1950	12, F	Lassitude; weakness (3 yr.)	Left: 40; Right: Not measurable	Not measurable	Systolic, from the xiphoid process to the pubis, posteriorly in the upper lumbar region
Goldzieher et al.[30] 1951	45, F	Attacks of nausea; vomiting; pressure in the neck; temporary unconsciousness (6 yr.)	115–60/ 80–100 During the attacks: up to 230	Right: not measurable Left: 300/180 (?)	...
Fisher and Corcoran,[19] 1952	14, M	Attacks of lancinating pains in the flanks (1 yr.); headache; disturbance of vision (1 mo.)	238/160	256/100	...
Glenn et al.,[13] 1952	19, F	Palpitations, precordial pains; dyspnea (9 yr.); epistaxis; headache; claudication	170–235/ 120	150/ 115–120	Systolic, in the epigastrium, posteriorly over the lower dorsal and the upper lumbar vertebrae
Albanese and Lazzarini,[20] 1953	12, F	...	240/160	...	Systolic, in the left epigastrium, posteriorly over 1st lumbar vertebra
Paramonova,[38] 1955	35, M	Claudication; precordial oppression ; headache (6 yr.)	220/120	140/90	Systolic, in the left epigastrium, posteriorly over 12th dorsal vertebra
Immon and Pollock,[17] 1956	32, F	Claudication (6 yr.); headache	210–220/ 110–140	100/—	Systolic, at the periumbilical region, posteriorly over dorsal vertebra
Martin and Yount,[39] 1956	32, M	Palpitations; headache (several years)	190/105	130/95	Systolic, in the mid-epigastrium, posteriorly from 12th dorsal vertebra to the sacrum
Miettinen et al.,[26] 1956	34, F	Claudication (from childhood); headache; vertigo (some months)	280/130	165/135	Systolic murmur and thrill at the umbilical region, posteriorly over 2nd lumbar vertebra

I
of the Abdominal Aorta Reported in the Literature

Aortic Pulsation in the Epigastrium	Palpable Collaterals	Notching of the Ribs	Anatomy and Localization of the Coarctation*
...	...	...	Coarctation, 1/2 inch in length, immediately below the renal arteries (A)
...	Internal mammary arteries, epigastric arteries	...	Aorta remarkably narrowed immediately after the visceral arteries. Iliac arteries hypoplastic (A)
Present	Right internal mammary artery, intercostal arteries at the inferior angle of both scapulae	Slight irregularity of the lower border of the ribs	Coarctation, 3 cm. in length and 8 mm. in diameter, 1 1/2 cm. below the renal arteries; lumen occluded by a thrombus; distal aorta hypoplastic (A)
...	Lower intercostal arteries	Present	Coarctation, minimum diameter of 2 mm., above and at the site of the renal arteries (A)
Present	Not present	Not present	Aorta hypoplastic below 1st lumbar vertebra; left renal artery hypoplastic (Ac, O)
...	7th to 12th intercostal arteries	Not present	Valve-like coarctation between the celiac axis and renal arteries; distal aorta and both subclavian arteries hypoplastic (A)
...	...	...	Aorta hypoplastic from the site of the renal arteries (O)
...	...	...	Coarctation, 2.5 cm. in diameter, at the level of the renal arteries; both renal arteries stenosed (Ao, A)
...	Not present	Not present	Coarctation, 10.5 cm. in length and 0.5 cm. in inner diameter, from 10th dorsal vertebra to 1st lumbar vertebra partly involving the celiac axis; Berry aneurysm of the right renal artery (Ao, O)
Present	...	10th ribs	Extreme coarctation, 5 to 6 cm. in length, from the celiac axis to the renal arteries; distal aorta and renal arteries hypoplastic (Ao, O)
...	Lower intercostal arteries, epigastric arteries	7th to 8th left ribs	Aorta hypoplastic, 12 mm. in diameter, below the celiac axis (O)
Present	...	...	Coarctation, 2 cm. in outer circumference, immediately below the renal arteries; distal aorta hypoplastic; thrombus in the coarctation (A)
...	Not present	...	Short coarctation at the site of the celiac axis (Ao)
Present	...	Not present	Aorta hypoplastic, "diameter that of a pencil," below the diaphragm (O)

* A = Autopsy. Ac = Angiocardiography. Ao = Aortography. O = Operation.

TABLE I

Essential Features of Twenty-Seven Cases of Coarctation

Author	Age (yr.) and Sex	Symptoms	Blood Pressure (mm. Hg)		Murmurs over the Abdomen and Back
			Upper Limbs	Lower Limbs	
Ritchie and Douglas,[10] 1956	47, M	Claudication(5 yr.)	140/109	Not measurable	...
Brust and Ferris,[21] 1957	14, M	None	180–240/140–180	Equal to the upper limbs	Systolic murmur and thrill over the abdomen and back
	24, F	Headache (3 mo.)	230–280/140–170	Equal to the upper limbs	Systolic murmur and thrill over the abdomen and back
Bunnag,[31] 1957	22, F	Claudication (several years)	140–144/70–80	Not measurable	Systolic murmur and thrill over the umbilical region
Schwartz et al.,[11] 1957	22, M	None	180–190/100–110	Not measurable	Systolic, in the midepigastrium, posteriorly over the upper lumbar spine
D'Abreu, et al.,[9] 1958	58, F	Claudication (16 yr.)	150/80	80/40	Systolic over the abdomen, posteriorly in the upper lumbar region
	40, M	Headache; dyspnea; claudication (5 yr.)	250/150	Not measurable	Systolic, in the epigastrium, posteriorly over the lower thoracic vertebrae
Gerbasi, et al.,[32] 1958	11, F	None	170–190/120–160	Not measurable	Continuous, in the left epigastrium, posteriorly over 10th dorsal vertebra
Loogen and Wetzels,[14] 1958	30, M	Headache; vertigo (7 yr.); coldness of the lower limbs	220–225/140–155	Not measurable	...
Mann and Gunter,[12] 1958	51, M	Congestive heart failure (3 yr.)	180/210/100/160	...	...
Milloy and Fell,[15] 1959	18, M	Claudication (since childhood); chest pain; headache (3 yr.)	180–210/120–130	110/80	Systolic, at the xiphoid angle
Shapiro,[18] 1959	10, M	Palpitations; coldness of the lower limbs	200–205/130	Not measurable	Systolic, at the xiphoid angle and over the back
Present authors	20, F	Claudication (5 yr.)	210–240/120–140	145–160/–	Continuous, in the left epigastrium, posteriorly over 12th dorsal vertebra

normal size at the level of the twelth thoracic vertebra (inner diameter 20 mm.). Between the first and second lumbar vertebrae it became narrow (inner diameter 9 mm.) and remained so to the site of the bifurcation which was located at the level of the fifth lumbar vertebra. The common iliac arteries were hypoplastic. Both renal arteries seemed normal and had their origin at the level of the first lumbar vertebra. The parenchyma of both kidneys had an intensive loading of the contrast medium in later

(*Continued*)
of the Abdominal Aorta Reported in the Literature

Aortic Pulsation in the Epigastrium	Palpable Collaterals	Notching of the Ribs	Anatomy and Localization of the Coarctation*
Not present	...	...	Aorta hypoplastic, 5 mm. in outer diameter, below 2nd lumbar vertebra
...	...	...	Short coarctation at the level of the renal arteries; both renal arteries stenosed (Ao, A)
...	...	...	Short coarctation at the level of the renal arteries; both renal arteries stenosed (Ao, A)
...	...	Not present	Coarctation, 4 cm. in length, at the level of 3rd and 4th lumbar vertebra (Ao)
....	Lower intercostal, subcostal and lumbar arteries, superior and inferior epigastric arteries	7th to 10th right ribs; 8th left rib	Aorta hypoplastic, 1/4 inch in diameter, below the diaphragm (Ao, O)
Not present	Not present	...	Coarctation, 2.5 cm. in length and 0.7 cm. in outer diameter, immediately below the renal arteries (Ao, O)
Not present	Lower intercostal arteries	9th to 10th ribs	Coarctation, 20 cm. in length, 0.8 cm. in outer diameter, from the level of 8th dorsal vertebra to 1 cm. below the renal arteries; celiac artery, superior mesenteric artery and renal arteries hypoplastic (O)
...	10th to 11th intercostal arteries	Not present	Aortic wall firm from 2 cm. below the diaphragm; outer diameter slightly narrowed; aortography demonstrated a remarkable intraluminal narrowing (Ao, O)
...	...	9th to 10th ribs	Coarctation, 7 cm. in length, from the level of the diaphragm; celiac axis involved (Ao, A)
...	In the lower thorax and abdomen	Probably in the 7th to 8th ribs	Aorta hypoplastic, 1 cm. in diameter below the renal arteries and occluded by a thrombus; iliac arteries and the left carotid artery hypoplastic (A)
...	...	Lower ribs	Coarctation, 7 cm. in length, from 1 inch above the diaphragm to below the renal arteries; arterial supply of the left kidney hypoplastic (O)
...	Not present	Minimal in the 10th to 12th ribs	Aorta hypoplastic, 0.7 to 1 cm. in diameter, below the celiac axis; both renal arteries stenosed and the right renal artery occluded by a thrombus (Ao, A)
Present	Not present	Not present	Aorta hypoplastic, 8 mm. in diameter, below 2nd lumbar vertebra

* A = Autopsy. Ao = Aortography. O = Operation.

x-ray films. There were numerous collateral vessels originating from enlarged and tortuous lower intercostal arteries and from the visceral arteries.

In connection with aortography, pressure tracings were recorded from the aorta above the constricted segment and during withdrawal of the catheter to the iliac artery. The aortic blood pressure above the coarctation was 210/110 mm. Hg and decreased suddenly to 140/100 mm. Hg at the site of the coarctation. The onset of the pulse wave in the

pressure curve from the iliac artery showed a delay of 0.06 second and the peak of the pulse wave a delay of 0.10 second as compared with the corresponding events in the pressure tracing from the aorta above the coarctation.

Surgical treatment of the aortic anomaly was considered impossible, because the whole distal abdominal aorta was hypoplastic. The patient was seen again in November 1958. Her condition had remained unchanged. The blood pressure in both arms was 250/140 mm. Hg and the systolic blood pressure in both legs was 185 mm. Hg.

Review of Reported Cases

Coarctation of the abdominal aorta was apparently first described by Quain[2] in 1847. To date, twenty-seven cases, including our own, have been reported in the literature. The essential features of these twenty-seven cases of coarctation of the abdominal aorta are summarized in Table I. Some cases which may be examples of coarctation of the abdominal aorta have not been included in this review because of incompleteness of anatomic or clinical data. Thus, for example, in the cases described by Doumer et al.[3] and Froment et al.,[4] aortography revealed a total obstruction of the upper abdominal aorta, but the anatomy of the distal abdominal aorta was unknown. In the two cases mentioned by Gliedman et al.,[5] the diagnosis was made on the basis of old records of autopsy and the clinical features were not known. In the cases reported by Wang[6] and Kusui et al.[7] it could not be decided whether the aortic obstruction found at autopsy was a congenital coarctation or whether it was caused by some acquired disease.

ETIOLOGY

Coarctation of the abdominal aorta is evidently a congenital anomaly, but the exact mechanism of its development is unknown. Maycock[8] suggested that coarctation of the abdominal aorta is due either to lack of or unequal fusion of the two dorsal aortas at one point with obliteration and loss of one of them, or to kinking of the fused aortas with consequent localized increased longitudinal tension producing a permanent narrowing. Maycock considered the first explanation to be the more probable.

ANATOMY

The classification proposed by D'Abreu et al.[9] is useful from the clinical and surgical point of view. These writers divide coarctations of the abdominal aorta into two groups: segmentary coarctations and hypoplastic coarctations. These two groups are further divided into three subgroups—suprarenal, interrenal and infrarenal coarctations—according to the site of the beginning of the narrowed aortic segment. *In the segmentary type* the coarctation consists of a localized stenosed segment below which the abdominal aorta again attains greater diameter. *In the hypoplastic type* there is no actual coarctation, but the abdominal aorta becomes narrow at a certain level and then remains hypoplastic down to the bifurcation. Some investigators have called the latter type of coarctation "atresia" [10,11] or "hypoplasia" [12] of the abdominal aorta.

In seventeen of the twenty-seven cases reported, the coarctation was of segmentary type: suprarenal in seven, interrenal in four and infrarenal in six. In four cases[9,13–15] a long coarctation involving the upper part of the abdominal aorta began above the diaphragm. In four of the sixteen cases the distal part of the aorta below the coarctation was stated to be hypoplastic. In one case a valve-like obstruction was observed at the site of the coarctation.[16] In ten of the twenty-seven cases, a hypoplastic type of coarctation occurred; the site of the aortic narrowing was suprarenal in five, interrenal in one and infrarenal in four cases.

The chief collateral anastomoses in cases of coarctation of the abdominal aorta originate from the lower intercostal arteries and internal mammary arteries to the caudal epigastric and lumbar arteries. Collateral networks may also develop between visceral arteries from both sides of the coarctation, especially between the superior and inferior mesenteric artery.

Although *degenerative and atherosclerotic lesions* may occur in the aorta proximal to the coarctation,[8,12,16–18] corresponding lesions are usually absent in the distal portion of the aorta. Thromboses may involve the stenosed aortic segment.[8,12,17] Microscopically, Fisher and Corcoran[19] observed thickening of the aortic intima and abnormal narrowing of the media at the site of the coarctation. Focal cystic necroses of the aortic wall occurred in the case described by Albanese and Lazzarini.[20]

The renal arteries and other major visceral arteries originating in the narrowed aortic segment may be stenosed,[18,19,21] hypoplastic[9,15,20,22] or occluded by thrombosis.[17,18] Anomalies of the major branches of the aortic arch occurred in two cases; in the case described by Kondo

et al.[16] both subclavian arteries were hypoplastic and the right subclavian artery had an anomalous origin, whereas in the case reported by Mann and Gunter[12] the left carotid artery was hypoplastic. Aneurysms of the cerebral arteries were found at autopsy in the case described by Fisher and Corcoran.[19]

HEMODYNAMICS

Hemodynamic consequences of coarctation of the abdominal aorta depend on the degree of aortic obstruction and on the amount of collateral circulation bypassing the narrowed aortic segment. As in cases of coarctation of the aortic isthmus, hypertension, both systolic and diastolic, is usually present in the arterial compartment proximal to the coarctation, whereas arterial pressure distal to the coarctation is normal or low.

Pathogenesis of Hypertension: There has been much discussion of the possible role of renal ischemia as a cause of hypertension in cases of coarctation of the aortic isthmus. Culbertson et al.[23] and Kirkendall et al.[24] were unable to find significant renal hemodynamic abnormalities in patients with coarctation of the aortic isthmus who were not in congestive heart failure. They suggested that hypertension in the upper arterial compartment is caused by mechanical factors and local regulatory mechanisms, rather than by a circulating humoral vasoconstrictor. The fact that hypertension may occur in cases of coarctation of the abdominal aorta in which coarctation is located below the level of the renal arteries supports the belief that impairment of the renal blood flow is not the cause of hypertension associated with coarctation.

As has been pointed out by Kirkendall et al.,[24] an important argument against the theory of renal ischemia as a causative factor in hypertension associated with coarctation is the clinical course of hypertension in patients with coarctation of the aorta. Severe retinopathy and other clinical symptoms of malignant hypertensive disease do not develop in patients with coarctation of the aortic isthmus unless there is an additional etiologic factor producing malignant hypertensive disease. Apparently, this is true in cases of coarctation of the abdominal aorta as well. However, the possibility exists that malignant hypertension due to renal ischemia may develop in some patients with coarctation of the abdominal aorta because the renal arteries may be stenosed or occluded by thrombosis. In four patients with coarctation of the abdominal aorta described in the literature,[17,19,21] severe retinopathy typical of malignant hypertensive disease did occur. Autopsy revealed impairment of the renal arterial blood supply caused by either stenosis or thrombosis of the renal arteries. In the case described by Milloy and Fell,[15] hypertension due to unilateral renal ischemia developed after a successful bypass operation.

CLINICAL FEATURES

Incidence: The true incidence of coarctation of the abdominal aorta is not known. The abdominal localization of coarctation is evidently not as rare as would appear from the small number of reported cases, because reports of new cases have appeared with increasing frequency; twenty-two of the twenty-six cases reported were diagnosed during the last ten years. Wood[25] has estimated that the abdominal aorta is involved in approximately 2 per cent of all cases of coarctation of the aorta. At the Hospital of the Wihuri Research Institute, seventy-two patients with coarctation of the aorta were examined in the period 1947 to 1958. In two cases, one of which has previously been reported by Miettinen et al.,[26] the coarctation was located in the abdominal aorta.

Sex Distribution: Fourteen of the twenty-seven patients were women and thirteen were men. This differs from the ratio of women to men in cases of coarctation of the aortic isthmus. According to Abbott[27] and Reifenstein et al.,[24] coarctation of the aortic isthmus occurs four to five times more frevuently in men than in women, but in the series of cases reported by Gross[29] and Wood[25] that ratio was only 2 to 1.

Symptoms: Most patients were free of symptoms during childhood and adolescence. Six of the eleven patients over thirty years of age were still asymptomatic at age thirty. Four patients did not have any symptoms until the fifth decade.

Intermittent claudication occurred in twelve of the twenty-seven patients; in addition, two patients complained of persistent coldness of the lower extremities. In two of the patients a trophic ulcer of the toe developed.[10,17] In four patients claudication was the only complaint. Intermittent claudication is said to occur in only 5 per cent of cases of coarctation

of the aortic isthmus.[25] The greater frequency of claudication in cases of coarctation of the abdominal aorta may be due to an inadequate development of the collateral circulation. Claudication was present since childhood in only two cases.[15,26] In other cases this symptom appeared between the ages of fifteen and forty-two. The appearance of claudication in the adult indicates that the blood supply to the lower extremities at that time becomes more seriously impaired. Degenerative and thrombotic lesions in the stenosed aortic segment and in the collateral anastomoses may have significance in the development of circulatory insufficiency of the lower extremities. In two cases[17,18] in which intermittent claudication did occur thrombotic obstruction of the aorta at the site of the coarctation was revealed at autopsy.

Other symptoms included headache (thirteen patients), precordial or epigastric pains (six patients), vertigo (four patients), palpitations (four patients), slight dyspnea on exertion (three patients), and epistaxis (one patient). Manifest congestive heart failure developed in four patients at the age of nine, thirty-four, forty-four and forty-nine. The patient described by Goldzieher et al.[30] had attacks closely simulating those caused by pheochromocytoma.

Physical Signs: The *blood pressure* in the arms is elevated; usually both the systolic and the diastolic levels are increased. However, cases in which blood pressure in the arms was normal have been reported.[9,10,31] The patient described by Goldzieher et al.[30] had paroxysmal attacks of hypertension; between these attacks, blood pressure was normal or slightly elevated. In the case reported by Kondo et al.[16] in which both subclavian arteries were hypoplastic, the blood pressure in the left arm was 40 mm. Hg; it could not be measured in the right arm.

The blood pressure is lower in the legs than in the arms; it may be unobtainable in the legs by the auscultatory technic. In cases of mild coarctation, blood pressure may be the same in arms and legs.[9,21] *Femoral pulsations* are usually poor and delayed or even impalpable; in mild cases, however, they do not differ greatly from normal. An important sign observed in some cases is the presence of *strong aortic pulsation in the epigastrium* and its sudden disappearance more distally. This sign is especially valuable in the differential diagnosis of coarctation of the abdominal aorta and coarctation of the thoracic aorta. In cases of coarctation of the abdominal aorta, visible or palpable pulsations of collateral arteries (if present) are observed in the lower intercostal spaces or on the abdominal wall.

A systolic murmur is heard above the coarctation, anteriorly in the left epigastrium and posteriorly at the level of the lower thoracic or upper lumbar vertebrae. In the case reported by Gerbasi et al.[32] and the one described herein the murmur above the coarctation was continuous, consisting of a louder systolic part and a faint decrescendo diastolic part. Spencer et al.[33] have recently paid attention to the occurrence of continuous murmurs in cases of coarctation of the aortic isthmus. The murmur arising from the stenosed aortic segment is continuous if the pressure gradient across the coarctation is both systolic and diastolic. This may occur in cases of severe coarctation if the collateral circulation bypassing the stenosed aortic segment is inadequate to maintain the diastolic blood pressure in the distal aorta at the same level as above the coarctation. The presence of both systolic and diastolic pressure gradients across the coarctation was demonstrated by direct pressure tracings from the aorta in the case reported herein.

Examination of the heart may reveal a heaving apex impulse suggesting left ventricular hypertrophy. Systolic murmurs at the apex or aortic area were recorded in sixteen cases. An aortic diastolic murmur, which is heard frequently in coarctation of the aortic isthmus,[25] was heard in only one case.

In uncomplicated cases of coarctation of the abdominal aorta, the *retinal arteries* are normal, or may show a slight narrowing and increased light streaking. In four of the fourteen cases in which ophthalmoscopic findings were mentioned, the retinal changes were typical of malignant hypertension. As has been mentioned, the development of malignant hypertension in these cases was evidently due to coexisting impairment of the renal arterial blood supply.

Roentgenographic and Other Special Examinations: Roentgenograms of the chest may reveal the heart to be of normal size, or with enlargement of the left chambers. Abnormalities of the aortic arch characteristic of coarctation of the aortic isthmus are absent. Notching of the inferior margins of the ribs, caused by tortuous and dilated intercostal arteries is observed in some cases, but only in the lower ribs. The presence or absence of notching of the ribs was

recorded in seventeen cases; in eight of these cases notching was observed in the seventh to tenth ribs.

The *electrocardiogram* revealed left ventricular hypertrophy in most cases, but was normal in some.

The exact anatomy of coarctation of the abdominal aorta is best revealed by *aortography*. Angiocardiography has been employed, but does not give sufficient contrast filling of the abdominal aorta and may lead to erroneous diagnosis. Aortography was performed in fourteen cases. An injection of the contrast substance in six cases was made through a needle inserted into the aorta by percutaneous puncture; in six cases the injection was made through a catheter introduced from the femoral artery into the abdominal aorta; in one case a retrograde injection through the left carotid artery was employed, and in another case the aortography was performed in connection with an exploratory operation. Aortography, however, may be a hazardous diagnostic procedure. Fatal complications occurred in two of the fourteen cases[18,21] and transient renal failure developed in one.[13]

Patients with coarctation of the abdominal aorta who have severe retinopathy or other features suggesting malignant hypertensive disease should be screened for the presence of *unilateral renal ischemia*. Nephrectomy may be of benefit in such cases. Special tests proposed for this purpose include, in addition to renal arteriography, examination of the flow of urine and sodium output of each kidney separately[1] and radioactive Diodrast® renograms.[34]

Differential Diagnosis: Differentiation of coarctation of the abdominal aorta and coarctation of the thoracic aorta is not difficult, if the possibility of abdominal localization of coarctation is kept in mind. Acquired conditions producing stenosis or occlusion of the abdominal aorta must also be considered in the differential diagnosis. These include atherosclerotic obstructive lesions with or without thrombosis, simple thrombosis or embolic occlusion, aneurysms or dissections involving the abdominal aorta, and external pressure from a tumor. As has been pointed out by Milloy and Fell,[15] local aortitis may also produce obstructive lesions of the aorta which are difficult to differentiate from congenital coarctation. Acquired, long-standing obstructive processes may sometimes give rise to the development of extensive collateral circulation, as was shown by Baylin.[35] Besides careful evaluation of the history and clinical findings, an aortogram is valuable in the differentiation of congenital coarctation of the abdominal aorta from acquired obstructive lesions.

PROGNOSIS

Twelve of the twenty-seven patients described in the literature died: two of them postoperatively, two from complications of aortography, and one from intestinal disease not related to coarctation. The patient described by Quain[2] died at the age of fifty after having epigastric pains on exertion during one year. The patient described by Power[36] died after a convulsive attack at the age of seventeen. The exact cause of death in these two cases is unknown. Two patients, aged eleven and fifty-one, died from congestive heart failure,[12,16] and three patients, aged fourteen, thirty-two and forty-six, from cerebrovascular accidents.[17,21,37] The majority of patients with coarctation of the aortic isthmus die before the age of forty, the average age of death being thirty-five.[28] The number of reported cases of coarctation of the abdominal aorta is so small that no certain conclusions can be drawn about the average life expectancy of patients with this anomaly. It seems, however, to be rather similar to the life expectancy of patients with coarctation of the aortic isthmus.

SURGICAL TREATMENT

Surgical treatment of coarctation of the abdominal aorta has been extensively discussed by D'Abreu et al.[9] As they pointed out, the possibilities of surgical treatment depend on the localization and length of the coarctation, its relation to the major visceral arteries and the state of the distal part of the aorta. Cases in which the distal aorta is extremely hypoplastic are evidently inoperable by reconstructive methods. Extensive thrombosis of the distal aorta also makes surgical treatment impossible. Resection of the stenosed aortic segment, with or without the use of a free arterial graft, may be feasible in cases in which a short segmentary coarctation occurs at the level of the diaphragm or below the level of the renal arteries. Unfortunately, coarctation of the abdominal aorta rarely is of this type.

Coarctation involving the aortic segment between the celiac axis and renal arteries presents an especially difficult surgical problem. Operations in which the stenosed aortic segment is bypassed

using the splenic artery or an arterial homograft, however, have given promising results. Such an operation was first described by Glenn et al.[13] who operated upon a patient with a coarctation involving the lower thoracic and upper abdominal aorta immediately proximal to the celiac axis. Splenectomy was performed and the enlarged splenic artery was inserted into the thoracic aorta proximal to the coarctation. Albanese and Lazzarini[20] operated upon a patient with an extreme coarctation extending from the celiac axis to the renal arteries. The aorta was divided at the distal end of the coarctation and a homologous arterial graft was inserted end-to-side into the aorta proximal to the coarctation and end-to-end into the distal part of the aorta. The patient died from postoperative anuria. Autopsy revealed an extreme hypoplasia of both renal arteries. In the case reported by Gerbasi et al.,[32] a segmentary coarctation limited to the celiac axis was bypassed using an aortic homograft. D'Abreu et al.[9] described two cases in which a bypass operation was accomplished. In the first case a short coarctation was located immediately below the renal arteries. After splenectomy, the splenic artery was lengthened by using an arterial homograft and then inserted into the aorta distal to the coarctation. In the second case a long coarctation extended from the lower thoracic aorta to a level immediately below the renal arteries. The aorta was divided at the proximal end of the coarctation and the bypass was accomplished using an aortic homograft. The central anastomosis was made end-to-end and the distal anastomosis end-to-side. In the case reported by Milloy and Fell[15] a coarctation extending from the lower thoracic aorta to a level below the renal arteries was bypassed using an aortic homograft.

Results of Surgery: Four of the five patients who were successfully operated upon using the bypass technic had hypertension. In three, the blood pressure decreased to normal after the operation. In the case described by Milloy and Fell[15] the blood pressure increased postoperatively. It became evident that this was due to unilateral renal ischemia. The left kidney which was supplied with small arteries originating from the stenosed aortic segment was removed and the blood pressure subsequently decreased. In this case, creation of a bypass evidently caused an impairment of the circulation in a previously ischemic kidney and precipitated the development of renal hypertension. Intermittent claudication, which occurred in four of the five patients operated upon, was abolished postoperatively in three patients and lessened in one patient.

In three cases[9,13,22] a bilateral thoracolumbar sympathectomy or splanchnicectomy was performed because of hypertension before the diagnosis of coarctation was made. Similarly, a lumbar sympathectomy was carried out in one case[17] because of intermittent claudication. No definite benefit resulted from these operations. In the cases described by Bahnson et al.[22] and Ritchie and Douglas,[10] a bilateral lumbar sympathectomy was performed because correction of the coarctation, which was of the hypoplastic type, was considered impossible. The operation had little or no effect on the symptoms of claudication. In the case reported by Paramonova,[38] the left kidney was decapsulated and embedded into omentum without benefit. In two cases,[19,21] nephrectomy was performed because hypertension caused by unilateral renal ischemia was considered to be present. The operation had no effect on the blood pressure and the patients died soon after the surgery. In both cases autopsy revealed bilateral stenosis of the renal arteries. In four cases the surgery was limited to exploratory operation.[11,14,26,30]

SUMMARY

A case of coarctation of the abdominal aorta occurring in a twenty-year old woman is reported and the essential clinical features of twenty-six cases reported in the literature are summarized.

In seventeen of the twenty-seven cases the coarctation consisted of a localized stenosed segment below which the aorta again attained greater diameter. In the remaining ten cases the coarctation was of the hypoplastic type; there was no actual coarctation, but the abdominal aorta narrowed at a certain level and then remained hypoplastic down to the bifurcation. In several cases the renal arteries or other major visceral arteries originating in the narrowed aortic segments were hypoplastic, stenosed or occluded by thrombosis.

Fourteen of the twenty-seven patients were women and thirteen were men. Most patients reached adult age without symptoms. The most common complaint was intermittent claudication and/or coldness of the lower limbs which occurred in fourteen cases. Hypertension in the upper limbs occurred in almost all

cases. Congestive heart failure and cerebrovascular accidents were the major complications encountered in the series.

The most important clinical feature in the diagnosis of coarctation of the abdominal aorta is the low location of the murmur. Evidence of collateral circulation, if present, is found in the lower part of the thorax and on the abdomen. Aortography is valuable in the evaluation of the anatomic quality of the coarctation and in the differentiation of this anomaly from acquired conditions producing stenosis of the abdominal aorta.

Malignant hypertensive disease may develop in some cases of coarctation of the abdominal aorta. Four cases of this kind have been reported in the literature; in all of them autopsy revealed impairment of the renal arterial blood supply either by stenosis or thrombosis of the renal arteries.

Surgical treatment of coarctation of the abdominal aorta is possible in selected cases. Operations in which the stenosed aortic segment is bypassed, using the splenic artery or an arterial homograft, have given promising results.

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ADDENDUM

Three papers dealing with coarctation of the abdominal aorta have appeared since the submission of our manuscript. Brust et al. (*Am. J. Med.*, 27: 793, 1959) have reported in detail two cases included in our review.[21] Hanson et al. (*Acta chir. scandinav.*, Suppl. 245: 315, 1959) have described a new surgical approach employed successfully in a case of coarctation involving the celiac axis and renal arteries. Morris et al. (*Arch. Surg.*, 80: 87, 1960) have described four cases; in two of them a successful surgical treatment was accomplished.

New Methods

A Modification of the Vasodilatation Test*

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AN INCREASINGLY important aid in determining the capacity for blood flow in the toes is the vasodilatation test, which measures blood flow when vasomotor tone is abolished and, in the presence of arterial occlusion, measures collateral circulation. The test aids prognosis and is often the determining factor in deciding whether or not arterial surgery, either grafting or endarterectomy, should be attempted.[1] If the test shows a good capacity for blood flow in the toes, the limb is in no immediate danger and a surgical procedure that in itself might compromise the circulation is contraindicated. If the test reveals a poor capacity for blood flow in the toes, the foot is in jeopardy and arterial surgery should be undertaken if feasible.

The increase in digital blood flow that results from heating the body was originally described by Lewis and Pickering[2] who noted the rise in temperature of a cool extremity when the body was warmed. Gibbon and Landis[3] modified the procedure for measuring the capacity for blood flow in the toes by immersing the forearms and hands of the subject in hot water in a thermoregulated room and measuring the temperature of the skin of the toes with thermocouples. (A room temperature of 20°C. maintains a satisfactory thermal gradient between skin and air.) From this procedure, it appeared that vasodilatation in the toes resulted from an increase in temperature of the vasomotor centers occasioned by warm blood from the immersed extremity. This phenomenon was not then used as a clinical test, but as a means of investigating the vasomotor innervation of the limbs. Gradually, however, the procedure came to be used as a means of determining the degree of obstructive vascular disease, which is now its main use.

Montgomery, Naide and Freeman[4] showed that amputation is seldom necessary when the final skin temperature in a test is above 26°C. and practically never when it is above 28°C. They used various methods of releasing vascular tone, including spinal anesthesia and other types of nerve blocks. Vasomotor tone is now released by heating the body, as well as the extremities that are not being studied, by applying heating pads and blankets in a room with a constant temperature of 20°C.[5] The flow in the extremities being studied is estimated by measuring skin temperature with thermocouples.

The average time of a vasodilatation test performed on a patient with ischemia is about two hours. Occasionally no vasodilatation occurs in three hours. In an attempt to speed up the test we adopted a method of releasing the vascular tone *initially* by warming the feet at the same time the body is being warmed by placing a heating pad close to *but not directly on* the feet and covering them with a blanket. Our purpose was to place the feet in a state of vasodilatation rather than in a state of vasoconstriction. We hoped to take advantage of the observation of Pickering and Hess[6] who noted that "with the feet initially at different temperatures vasodilatation is delayed in the cooler."

Also we had previously found that elevating the head of the patient's bed seems to cause an increase in blood flow to the feet because it promotes an increase in the oxygen tension of ischemic toes.[7] Therefore, we studied the effect of elevating the head of the bed as well as that

* From the Vascular Section of the Edward Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania. The expense of the tests was defrayed by The John A. Hartford Foundation, Inc.

TABLE

Differences in Time, Final Temperature and Final Blood Flow of

Patient	Sex and Age (yr.)	*Method A*											
		Time (min.)	Toe Temperature (C.)						Room Temperature (C.)	Oral Temperature (F.)		Time (min.)	
			Right			Left							
			1st	3rd	5th	1st	3rd	5th		Start	End		1st
F. H.	M, 64	80	32.0	33.5	34.0	24.0	24.0	26.0	20.2	98.0	99.0	65	33.0
J. M.	M, 65	70	22.0	22.5	23.0	22.0	22.5	25.5	19.5	98.6	99.0	55	27.0
G. T.	M, 70	115	—	—	—	27.0	25.5	27.5	20.0	98.6	—	110	—
H. B.	F, 61	180	28.0	27.0	27.5	26.0	24.0	26.0	20.0	98.8	98.8	105	29.0
M. B.	F, 49	130	—	—	—	30.0	28.0	28.0	20.0	97.8	98.2	90	—
E. S.	M, 59	115	28.0	29.5	29.5	28.0	29.5	30.5	19.5	97.8	98.8	100	31.0
R. M.	M, 78	115	21.5	21.5	22.5	21.5	22.0	22.0	20.5	97.6	98.4	90	23.5
F. R.	M, 58	110	23.0	23.5	25.0	23.5	24.5	23.0	20.5	98.4	98.8	100	23.0
E. E.	M, 52	90	21.0	21.5	21.5	21.5	21.5	22.0	21.8	98.0	99.0	75	23.5
Mean	62	112							20.2	98.2	98.8	88	

NOTE: In method A vasodilatation is produced by applying heat to the abdomen. In method B vasodilatation calculated from a graph by Felder et al.[8]

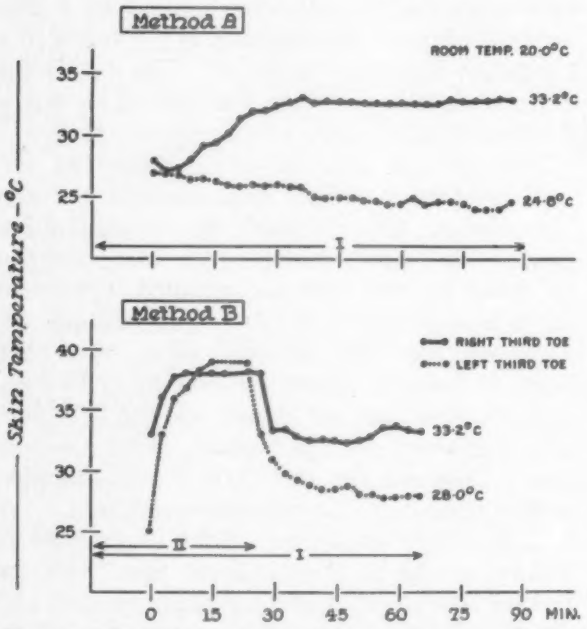


FIG. 1. Method A, chart of skin temperature of the third toes during a vasodilatation test in which the vasodilatation was produced by applying heat to the abdomen (I) only. Method B, chart of skin temperature of the third toes during a vasodilatation test in which the vasodilatation was produced by applying heat to the abdomen (I) and the feet (II). Both tests were performed on the same patient. Note that method B resulted in a greater degree of vasodilatation than method A in the left third toe. In the right third toe there was no essential difference in vasodilatation between the two methods. In both feet vasodilatation occurred more rapidly in method B.

of initially warming the feet during the vasodilatation test.

The purpose of the present study is to investigate the effects of these two conditions on the reliability and speed with which a vasodilatation test can be performed.

METHOD

All the various procedures were used on sixteen patients (thirteen men and three women) who had arteriosclerosis with some grade of arterial occlusion in one leg. Their ages ranged from forty-nine to seventy-eight years, with a mean of sixty-one. After an adequate meal and emptying of the bladder, each subject lay on a comfortable bed in a 20°C. thermoregulated room. In all cases their arms and bodies were heated with two blankets and two heating pads throughout the study. Thermocouples for recording temperatures of the skin at intervals of three minutes were placed on the first, third and fifth toes of both feet. Oral temperature was recorded at the beginning and end of each test.

In the first series, two methods of testing, A and B, were applied to each of nine patients (Fig. 1). In method A the feet were exposed to room air throughout the entire procedure and the test was continued until it was believed that maximum vasodilatation had occurred. In method B a heating pad was placed *close to but not touching* the feet and a blanket was placed over both the heating pad and the feet for fifteen minutes or until the temperature of the toes as measured by the thermocouples had reached 38°C. The feet were then

I

Toes Between Two Methods of Performing the Vasodilatation Test

Method B								Time Difference Between B-A (min.)	Average Difference in Toe Temperature (c.) Between B-A		Approximate Difference in Flow (cc./100 cc. tissue/min.) Between B-A	
Toe Temperature (c.)					Room Temperature (c.)	Oral Temperature (f.)						
Right		Left										
3rd	5th	1st	3rd	5th		Start	End		Right	Left	Right	Left
33.0	33.0	28.0	28.5	29.0	20.0	97.0	98.8	−15	0	4.0	0	6
28.5	28.5	27.0	27.0	26.0	19.0	99.4	99.4	−15	5.5	3.3	7	6
—	—	25.5	24.5	26.5	19.0	98.0	98.2	− 5	—	−1.2	—	0
29.5	30.5	27.0	28.0	29.0	20.0	98.6	98.8	−75	1.2	3.8	4.5	6
—	—	29.0	29.0	29.0	19.0	97.0	98.0	−40	—	0.3	—	3
31.0	31.5	28.5	28.5	29.5	20.0	98.0	—	−15	2.0	0	11	0
24.0	24.5	25.0	25.5	26.0	20.0	97.6	97.0	−25	2.2	4.0	1	3
23.5	23.5	24.0	25.0	25.0	20.0	98.0	98.4	−10	−0.5	0.8	0	1
24.0	25.0	26.0	26.0	26.5	21.0	98.0	98.2	−15	2.5	4.6	1	3
					19.8	98.0	98.5	−24	1.8	2.2		

is produced by heating the feet directly and applying heat to the abdomen. Approximate blood flows were

exposed to the air with the heating pad and blanket removed. The test was continued until the temperature of the toes remained constant for a half hour. The tests were performed on each of the nine patients within a three-week period, six being subjected to method A first and three to method B first.

A further series of observations was made on seven patients to observe the effect of elevating the head of the bed. Two tests, using method B, were performed on each patient. In one test the head of the bed was elevated on 8-inch blocks and in the other the bed was kept horizontal.

TABLE II

Differences in Final Results of Vasodilatation Test Produced by Inserting 8 Inch Blocks Under Legs at Head of Bed

Patient	Sex and Age (yr.)	Head of Bed Up				Bed Horizontal				Average Difference in Toe Temperature 1 minus 2	Approximate Difference in Flow (cc./100 cc. tissue/min.) in Toes
		Toe Temperature (c.)*	Room Temperature (c.)	Oral Temperature (f.)		Toe Temperature (c.)*	Room Temperature (c.)	Oral Temperature (f.)			
				Start	End			Start	End		
H. G.	M, 52	29.8	19.4	98.0	98.2	29.4	19.0	98.0	98.0	0.4	3
C. C.	M, 55	30.8	20.5	98.2	98.4	30.4	20.0	98.8	98.6	0.4	5
F. R.	M, 58	28.3	20.0	98.0	98.4	27.8	20.0	98.6	98.8	0.5	2
T. J.	M, 49	30.8	20.0	98.2	98.0	26.9	19.5	98.4	98.8	3.9	12
D. H.	F, 67	32.1	20.0	97.4	97.8	30.5	20.0	97.4	98.6	1.6	25
J. D.	M, 68	31.6	20.0	98.4	98.6	31.1	20.5	98.2	98.6	0.5	14
A. W.	M, 68	27.3	19.5	99.4	100.2	26.9	20.0	98.4	98.6	0.4	2
Mean	60	30.1	19.9	98.2	98.6	29.0	19.9	98.3	98.5	1.1	

NOTE: In all cases the feet were pre-heated as described in method B. Approximate blood flows were calculated from a graph by Felder et al.[8]

* Average of 1st, 3rd and 5th toes of both feet.

Results

The results of method B in which the feet were pre-heated were compared with those of method A in which the feet were not pre-heated. Method B was invariably faster by an average of twenty-four minutes and produced a fuller degree of vasodilatation in all but one instance in which there was no appreciable difference between the two methods (Table I).

Using method B exclusively and comparing the final state of vasodilatation in the "head-up" position with the same state in the horizontal position it was found that a fuller degree of vasodilatation was obtained in the "head-up" position in all seven patients (Table II).

Comments

In view of the observation of Pickering and Hess[6] that "warming the body produces . . . in the lower extremities incomplete loss of vasoconstrictor tone," and that in an environment of 20°C. vasodilatation is considerably more difficult to produce than vasoconstriction, it was hardly surprising to find that pre-heating the feet produced a more complete and more rapid state of vasodilatation.

In our previous observations showing that the oxygen tension of the toes was increased when the head of the patient's bed was raised, the feet had purposely been kept less than fully vasodilated and only suggestive evidence of increased blood flow was obtained.[7] In the studies described here, when a full state of vasodilatation was present increased blood flow in the feet was clearly indicated when the head of the bed was raised.

We have defined the vasodilatation test as the measurement of blood flow when vascular tone is abolished. The combination of complete abolition of vascular tone and simultaneous measurement of the resulting blood flow by comfortable and practical means is not often possible. Our modifications, however, do serve to reduce vascular tone more completely and furnish a more satisfactory test.

Conclusions

The modification of the vasodilatation test described results in a greater degree of vasodilatation and can be administered in less time than previous procedures.

Summary

The vasodilatation test, the measurement of blood flow when vasomotor tone is abolished, can be a determining factor in deciding whether or not arterial surgery should be attempted. The purpose of this work is to show the advantages in time, and usually in accuracy, of placing patients in a state of vasodilatation when performing the test. An advantage gained by allowing the feet to be in a slightly dependent position is also demonstrated.

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The Application of the Segmental Plethysmograph to the Measurement of Blood Flow Through the Limbs of Human Beings*

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THE measurement of blood flow through the extremities of man has become a routine determination in recent years. The standard procedure is to use a plethysmograph, usually in some form derived from that originally described by Hewlett and van Zwaluwenburg.[1] These systems require a rigid, non-distensible jacket arranged in such a way that any increase in the volume of the limb displaces some fluid from the space between the jacket and the skin into a volume sensitive recording device. Although water or air may be used to fill the space, in the usual laboratory models the system is water-filled. Because of the rigidity of the case and the weight of the water such an instrument is not entirely suitable for the measurement of blood flow in the *moving subject*.

The problem of measuring blood flow under this special circumstance has been given much attention in recent years and several ingenious solutions have been proposed. The impedance plethysmograph, which requires the application of only two simple electrodes to the extremity and which is therefore easily carried on the active subject, has been suggested by Nyboer,[2] and more recently studied by Powers et al.[3] Unfortunately this instrument is difficult to calibrate and the resulting values cannot easily be translated into the dimensions of a flow, namely, volume of blood flowing through unit tissue per unit time. Whitney,[4] in 1953, described the so-called strain gauge plethysmograph which measures the circumference of various portions of the limb. By geometric conversion, changes in circumference can be related to changes in volume. Although these measurements have been reproducible under some conditions,[5] they do not represent a *direct* measurement of volume. Recently Dohn et al.[6] and Graf and Westersten[7] have suggested that an air-filled flexible cuff might be placed around a segment of the extremity and be connected to a sufficiently sensitive volume transducer to serve as a plethysmograph.

The purpose of this report is to call attention to the fact that the segmental plethysmograph† recently described by one of us[8] can be applied to this measurement of blood flow in the human extremity.

Ideally, the plethysmograph for measurement of blood flow in the extremity should satisfy certain requirements. The cuff or enclosing chamber should be designed to present a rigid surface; to permit ease in application and to impose minimum interference with the subject, it should be light and of such a nature as to conform quickly and easily to variously shaped limbs. To assure accurate registration the detector should respond to minute increments in volume of segment; it should function as a volume rather than a pressure sensitive system; that is, increase in the volume of the forearm should result in minimum pressure changes since these in themselves can modify the apparent volume increments. The total pressure in the cuff should be held as low as practical.

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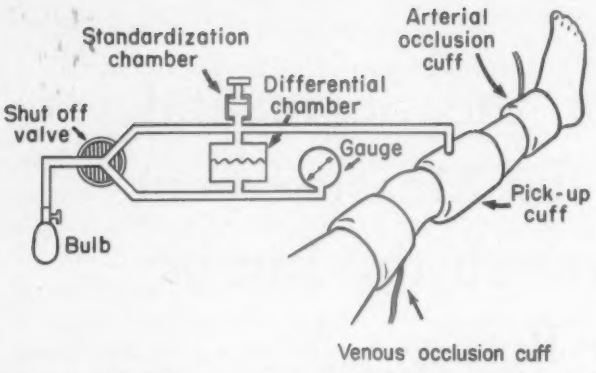


FIG. 1. Arrangement of segmental plethysmograph for measurement of blood flow in the calf by venous occlusion technic. Displacement of the diaphragm of the differential chamber is proportional to the change in volume of the pick-up cuff; the diaphragm is one plate of a modified capacitance manometer connected to a suitable amplifier and recording system.

Obviously the system as a whole must be linear; that is, the final output should give an equal displacement per unit volume change over its entire range. This is assured by using the mid-portion of the sensitivity range of the transducers and amplifiers involved in the system. The frequency response requirements for venous occlusion plethysmography are far less rigorous than those for the detection and accurate writing of the pulse amplitude curves; usually 5 to 10 c.p.s. is ample. Finally, the system should be simple to calibrate in terms of (1) the change in output per unit change in the arm volume and (2) the total volume of tissue actually contained within the plethysmograph. The first calibration is accomplished by introducing a measured volume of air or fluid into some part of the system and noting the effect on the final written record. The total volume of extremity contained in the plethysmograph is measured by fluid displacement.

Most of these requirements are fully satisfied by the segmental plethysmograph. Since this instrument is designed to give an accurate quantitative measure of the volume of the pulse in a segment of extremity, it is already equipped with a transducer with characteristics suited to measurement of the volume increment following venous occlusion, except that the increase in segment volume in the course of a venous occlusion flow determination, eight to fifteen times as large as a single pulse, might extend beyond the linear range of the detector. To test this possibility and to assure ourselves that all the other characteristics of the segmental plethysmograph were indeed suitable for blood flow determinations, the following experimental studies were undertaken.

METHOD

The cuff used as a detector to determine blood flow was wrapped around an extremity in exactly the same way as when used for an oscillometric determination. A few preliminary studies indicated that the cuff used must have a highly flexible membrane against the skin and a more rigid external membrane, and that it should be shaped to assure

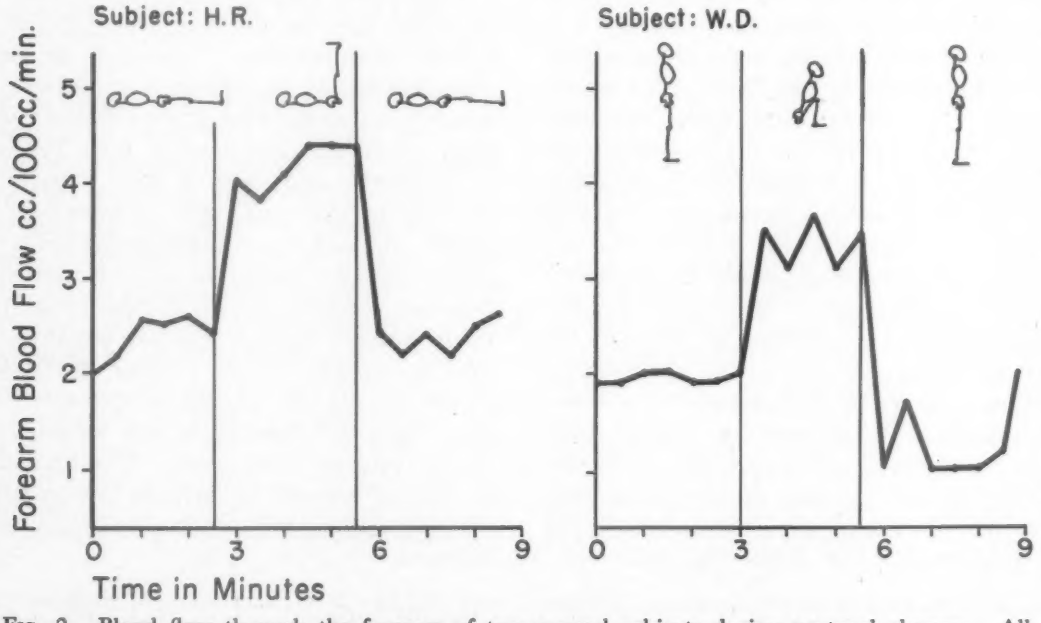


FIG. 2. Blood flow through the forearm of two normal subjects during postural changes. All determinations were made using the segmental plethysmograph.

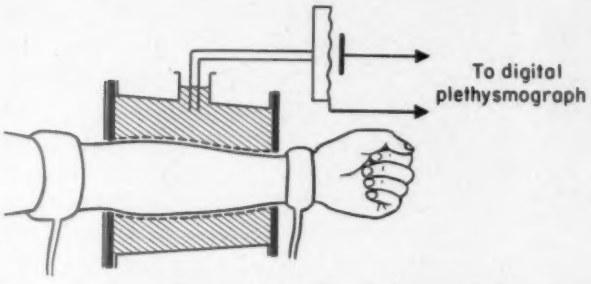


FIG. 3. Arrangements for blood flow measurement using the water-filled plethysmograph adapted to record through a digital transducer.

close approximation to the surface of the extremity. A suitable cuff of light dental dam was prepared to form a section of a cone when wrapped around the extremity; the rubber cuff was held in place with elastic tape and covered with a non-distensible leather or plastic band that served as the rigid external surface. Changing the tension with which the cuff was applied did not significantly change the resulting venous occlusion record.

Ordinary sphygmomanometer cuffs were used to obtain arterial occlusion distal to the detector and venous occlusion proximal to the detector. For the determinations the "plethysmographic" cuff was inflated to a pressure between 10 and 20 mm. Hg and isolated from the reference chamber by the "shut-off" valve. Varying pressures over this range did not alter measured blood flow. The arterial occlusion cuff was inflated to a pressure above systolic and, after fifteen to forty-five seconds,

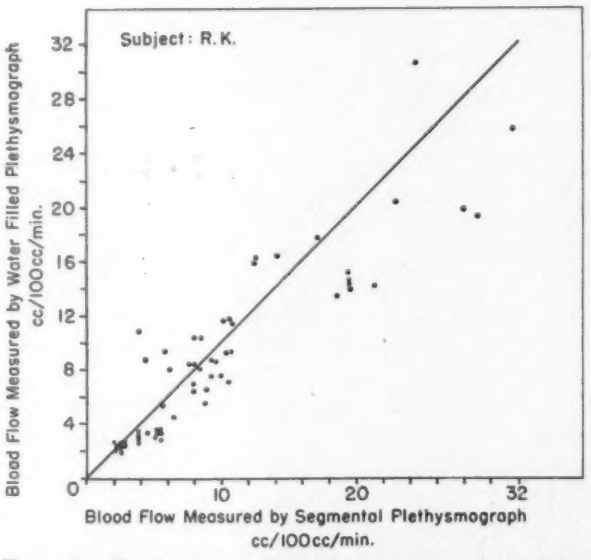


FIG. 4. Comparison of simultaneously determined flows on the forearms of a normal subject. Ordinate: flow measured by the water-filled plethysmograph; abscissa: measurements by the segmental plethysmograph. Part of the scatter of the points around the line of 1:1 correspondence represents the asymmetry between the two arms.

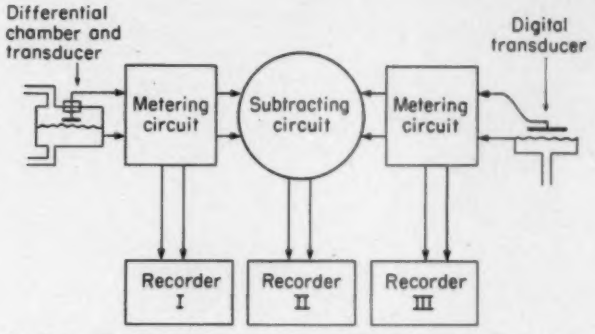


FIG. 5. Block diagram of arrangements for the electrical comparison of the output from the two plethysmographs.

the venous occlusion cuff was acutely inflated to a pressure between 60 and 80 mm. Hg. The increase in volume of the extremity underneath the segmental cuff was then followed on a suitable recording galvanometer. These arrangements are shown in Figure 1.

RESULTS

Using this system the apparent flows through the forearm were determined on subjects at rest and during periods of altered vasomotor tone induced by local exercise, reactive hyperemia and postural shifts. In all cases the data showed the changes to be the same as those encountered when measurements are made with the water-filled plethysmograph. In Figure 2 the changes in blood flow during several postural changes are plotted. The increase in flow when the legs of a supine subject are passively raised is about the same as that reported by Roddie, Shepherd and Whelan;[9] the change in flow in the forearm of the squatting subject corresponds to that described by Sharpey-Schafer et al.[10]

Direct comparisons were made of the blood flows as measured by the segmental plethysmograph on one forearm as described and as measured by a conventional water-filled plethysmograph (similar to that used by Barcroft and Swan[11]) placed on the contralateral arm. To facilitate comparison of records drawn by the two plethysmographs, the conventional instrument was arranged to activate a simple digital plethysmographic transducer[12] as shown in Figure 3. The detector was connected to an open-ended tube dipping into the water in the chimney to make the sensitive digital plethysmograph suitable for measuring changes in volume of the arm. The output from the two plethysmographs can thus be compared easily. Several hundred pairs of determinations have been made on ten subjects under varying conditions, and the

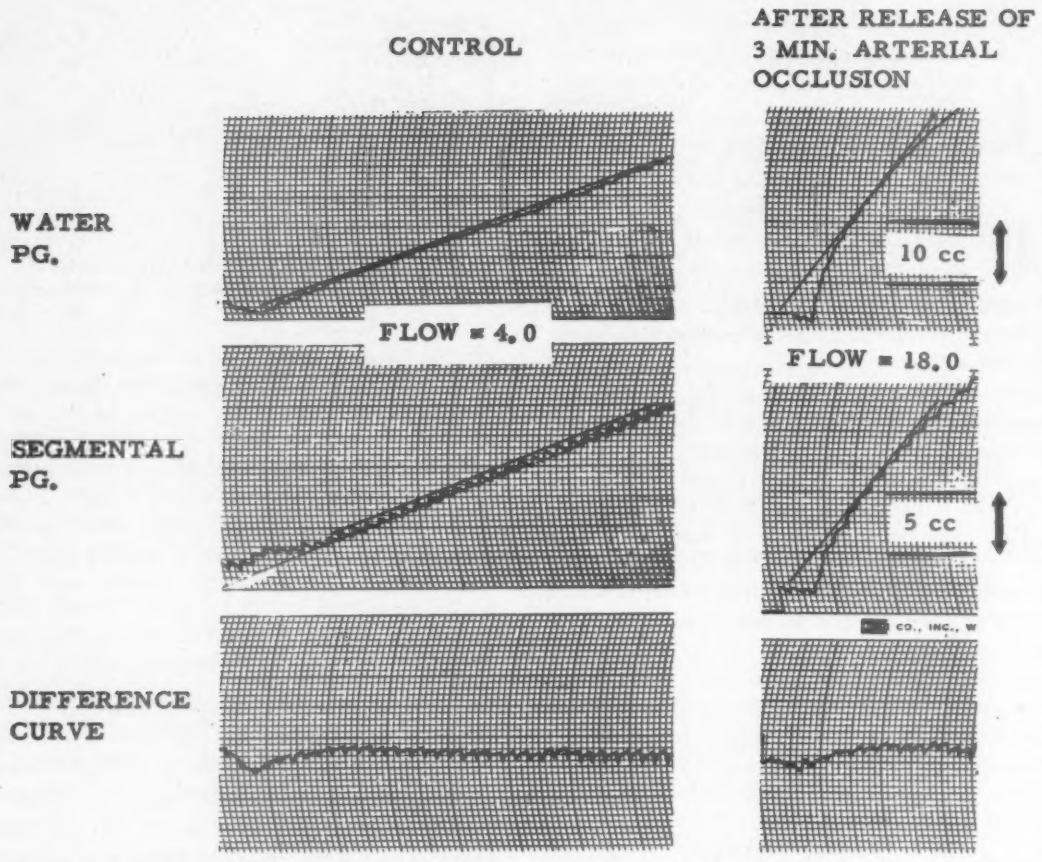


FIG. 6. Tracings of changes in forearm volume after venous occlusion obtained with traditional water and segmental plethysmographic technics. Equal increases in muscle blood flow during reactive hyperemia are shown by both technics. Note that the "difference curve" showed no significant deviation from base line (zero) level in either the control or hyperemic flow determination. Units of flow = cc. per 100 cc. of tissue per minute.

blood flows as estimated by the two technics correspond fairly well. A plot of such data in a single subject is included in Figure 4.

A more direct demonstration of the validity of the segmental measuring method and the extent to which it corresponds with the water-filled system was made using the electric comparison system diagrammed in Figure 5. The two plethysmographic outputs are fed to a subtraction circuit with all factors arranged to give zero output during bilateral venous occlusion in the control situation. With symmetrical changes in blood flow, there should be an increase or decrease in the output of both the independent metering circuits; but the difference between them should remain zero. Measurements were made of the blood flow at rest, after equal periods of arterial occlusion of the two extremities and after the administration of vasodilator drugs. Output of the subtraction circuit showed minimal drift with blood flow changes from 4 to 20 cc. per 100 cc. of tissue per minute, as demonstrated in Figure 6.

The data presented establish the correspondence of the two systems and therefore demonstrate the applicability of the segmental plethysmograph to the problem of measuring blood flow in the extremities. The ease with which the segmental plethysmographic cuff can be placed on the limb and the freedom from movement artifacts correspond to the advantages that have been so clearly set forth by Graf and Westersen[7] and Dohn et al.[6] in their recent papers.

SUMMARY

A simple, accurate method for the plethysmographic measurement of blood flow in the extremities of human subjects makes use of the "segmental plethysmograph," which can be placed on moving subjects with recordings made immediately after movement. The system in-

volves an air-filled cuff which can be wrapped around any portion of the extremity, and a sensitive, balanced volume transducer which can be readily and accurately calibrated against a standard volume increment. Direct comparisons of the present system and the classic water-filled plethysmograph yield satisfactory results. The chief advantages of the present technic are simplicity of application and adaptability to moving subjects.

Acknowledgment

Sally Cody, James Arthur, Patrick Humphreys and Don Trotter must be thanked for their active role in the accumulation of the data on which this report is based. Mr. Chester Smith helped to devise the original equipment and modify it for the present use.

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Case Reports

Metastatic Leiomyosarcoma of the Heart*

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WHILE general articles dealing with metastatic tumors of the heart do list the uterus as being the primary site,[1,4,5,8,9,14,15] a search of the indexed literature has failed to reveal any specific case report of cardiac invasion by metastatic uterine leiomyosarcoma. The present report concerns the clinical and pathologic findings in a patient with this disease.

CASE REPORT

A forty-two year old Negro woman entered the hospital on April 9, 1958, because of a hacking, nonproductive cough and shortness of breath of two months' duration. At first dyspnea was noted only on moderate exertion, such as walking rapidly; however, it progressed until it was present even at rest one week before hospitalization and was associated with two pillow orthopnea. Since the first part of the year the patient had had occasional elevations in temperature and had lost 50 pounds in body weight.

The patient had undergone a total hysterectomy with bilateral salpingo-öophorectomy in February 1954 at another institution. At the time of hospitalization for her terminal illness, the pathologic findings were not known.

Physical Findings: On admission she was orthopneic and acutely, as well as chronically, ill. The neck veins were distended to the angles of the jaws at 30 degrees. The pulse rate was 110 per minute. The blood pressure was 130/80 mm. Hg in both arms without evidence of pulsus paradoxicus. Crepitant inspiratory rales were present throughout both lung fields. Flatness to percussion was elicited over the bases of both lungs; tactile and vocal fremitus were decreased over these same areas. The heart was enlarged to the left. There was a protodiastolic gallop at the apex. A high-pitched, squeaky systolic murmur was present over the entire precordium, being best heard along the left sternal border and transmitted to the left axilla. A systolic thrill was felt over the apex. The second aortic sound was slightly diminished. The liver was palpable 4 fingerbreadths below the right costal margin, its edge being smooth and slightly tender. A hepatojugular reflux was present.

A clinical diagnosis of rheumatic heart disease, aortic stenosis and mitral insufficiency with congestive heart failure was made. Subacute bacterial endocarditis and disseminated lupus erythematosus were also considered.

Radiographic and fluoroscopic examination of the chest revealed generalized marked cardiac enlargement and was suggestive of pericardial effusion (Fig. 1). An electrocardiogram showed sinus tachycardia (100 per minute) and low amplitude of all complexes. Urinalysis, blood chemistry determinations, hemogram and liver function tests were within normal limits. Blood cultures and L. E. cell preparations were negative.

Course: In spite of conventional treatment, in-



FIG. 1. Posteroanterior view of chest demonstrating generalized cardiac enlargement and pulmonary congestion.

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FIG. 2. Gross illustration of posterior surface of heart. Note bulging tumor mass above atrioventricular sulcus.



FIG. 3. Gross view of heart. Gray-white papillary tumor is seen growing along surface of tricuspid valve.

tractable congestive heart failure persisted and the patient's condition deteriorated rapidly. The murmur and thrill varied in intensity and at times completely disappeared. On the second hospital day a pericardial friction rub was heard transiently and a pericardiocentesis was performed; however, no fluid was obtained. Recurrent transitory arrhythmias, including nodal tachycardia, paroxysmal atrial fibrillation and bigeminy, appeared and were attributed to intolerance to digitalis. On the thirteenth hospital day sharp pains developed in the right side of the chest and the patient coughed up some bright red blood. She became febrile and stuporous and died in coma on the sixteenth hospital day.

Postmortem Findings: At autopsy the heart weighed 480 gm. A large, bulging, nodular, yellowish gray tumor mass, measuring 74 by 63 by 35 mm., was present along the posterior surface of the heart just above the atrioventricular sulcus (Fig. 2). On opening the right side of the heart a polypoid tumor, measuring 62 by 42 by 33 mm., was seen arising from the opening of the coronary sinus and extending downward through the tricuspid orifice for a distance of 26 mm. (Fig. 3). A similar tumor mass 16 by 18 by 4 mm. was attached to the endocardium of the lateral margin of the right ventricle. A polypoid fungating mass similar to the two described, measuring 68 by 52 by 56 mm., was found arising from the posterior wall of the left atrium. It extended through the mitral valve. All chambers of the heart were extremely dilated and the entire myocardium presented a yellowish tan appearance. Mural thrombi were present in the atrial appendages. At the anterior margin of the inferior border of the upper lobe of the

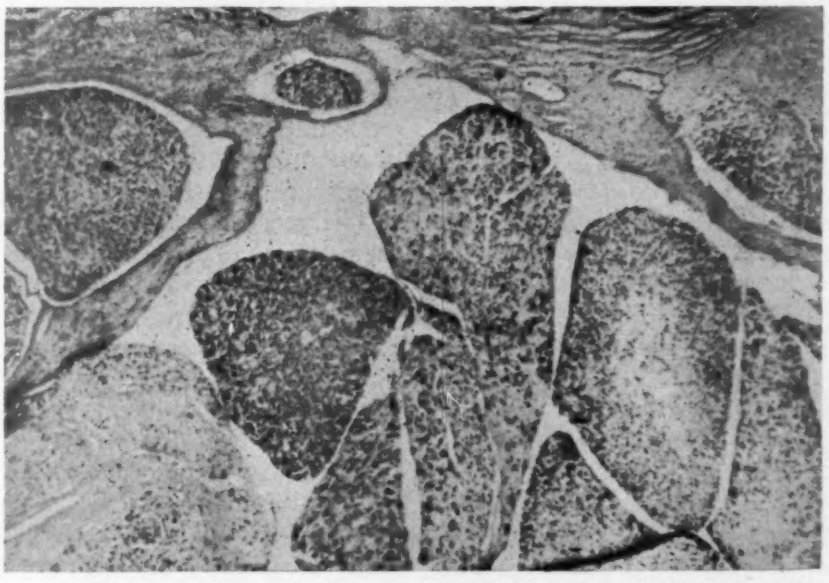


FIG. 4. Photomicrograph of papillary tumor growth in right atrium. Original magnification × 75.



FIG. 5. Photomicrograph of metastatic tumor in wall of left atrium. Original magnification × 75.

left lung an umbilicated, firm nodule measuring approximately 32 mm. in diameter was found; a similar nodule was present in the anterior portion of the lingula. No tumor was found elsewhere.

Microscopic examination of the left atrial appendage revealed the lumen filled with a laminated antemortem thrombus (Fig. 4). Around the periphery of the thrombus occasional tiny clusters of spindle-shaped malignant cells were seen. Sections of the tricuspid and mitral valves showed papillary growths composed of similar malignant cells arranged in whorls and interlacing strands with poorly demarcated boundaries and sparse amounts of bright eosinophilic-staining cytoplasm. The nuclei varied greatly in size and shape, many being gigantic and hyperchromatic. In rare cells longitudinal myofibrils were seen. Mitotic figures were observed occasionally. The central portions of many of the tumor areas showed massive necrosis. The nodules in the lung contained malignant cells similar to those described in the tumor tissue found in the heart (Fig. 5). Findings typical of pulmonary infarction were found in the lower lobe of the right lung.

Review of the sections from the uterus made in 1954 showed tumor tissue identical to that described herein.

The final pathologic diagnosis was metastatic leiomyosarcoma of the heart and left lung.

COMMENTS

Cardiac involvement by metastatic malignancy is more common than it was once considered; the incidence of such involvement ranges from 5 to 20 per cent of all patients dying of cancer.[2,7,9] Cancer of the breast, bronchogenic carcinoma, malignant melanoma and malignant lymphoma constitute the most frequent primary lesions;[6,7] occasionally uterine and ovarian carcinomas metastasize to the heart.[1,8,9,11,14] In some 2,600 instances of cardiac involvement by metastatic tumor in a group of 750,000 cases studied at the Armed Forces Institute of Pathology only six instances of cardiac metastases by uterine leiomyosarcoma were encountered.[16]

Metastatic malignancy of the heart should be suspected in patients with known malignant disease in whom cardiac dysfunction develops, such as heart failure refractory to accepted therapy, arrhythmias, conduction defects, pericardial effusion, pericardial friction rub and roentgenographic evidence of unusual cardiac silhouette.[6,7,10] Electrocardiographic changes in patients with metastatic heart tumors are, for the most part, non-specific or entirely lacking.[9] Arrhythmias are not uncommon, being predominantly of atrial origin and including premature contractions, flutter and fibrillation.[3,7]

The mechanism of cardiac involvement by metastatic tumor cells includes four possible routes:[4] direct extension from the lungs or mediastinal structures, hematogenous dissemination via the coronary arteries, implantation of tumor on to endocardial surfaces and lymphatic spread via the tracheobronchial lymph nodes.

The rarity of cardiac metastases from leiomyosarcoma of the uterus, along with the time interval between surgical removal of the primary tumor and the appearance of congestive heart failure in this case, led us to give more

serious consideration to the more common types of acquired heart disease. The arrhythmias were probably due to myocardial invasion by tumor cells into the atrial muscle and the atrioventricular node in particular rather than to intolerance to digitalis. The changing murmurs, while not unusual in proliferating intracardiac mass lesions, in this case probably reflected progressive involvement of the mitral valve by the metastatic tumor. Of the possible routes for cardiac involvement by metastastic tumor cells, it would appear that in this case hematogenous dissemination via the coronary arteries occurred.

It is unlikely that correct antemortem diagnosis in our patient would have altered the treatment or outcome. However, in patients with other tumors appropriate therapy could offer varied benefits.[12,13]

Summary

A clinicopathologic study of a patient with metastatic leiomyosarcoma involving the heart is presented. The primary tumor was found in the myometrium when the uterus was surgically removed three years prior to the onset of cardiac manifestations. The clinical course was dominated by severe cardiac enlargement, bizarre arrhythmias and intractable congestive heart failure, mimicking rheumatic heart disease and digitalis intoxication. We have speculated upon the probable route of metastasis.

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The Low Salt Syndrome

An Extreme Example in Heart Failure*

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A sixty-seven year old white woman, known to have rheumatic heart disease, was admitted to St. Vincent's Hospital on January 28, 1958. Her chief complaint on admission was increasing shortness of breath, edema of the ankles and a spasmodic cough productive of yellow sputum, which had developed over a period of five days. She had been admitted on two previous occasions to the hospital because of severe congestive heart failure with left pleural effusion. In the interim, she had been treated in the outpatient department with digoxin and weekly mercurial injections.

On admission to the hospital, physical examination revealed a thin, elderly woman, chronically ill and suffering from acute respiratory distress. The blood pressure was 128/78 mm. Hg; pulse 100 and irregular, rate 42 per minute; the temperature was 103°F. Cyanosis of the lips and nailbeds was evident. There was some congestion in the pharynx and the neck veins were distended. Examination of the chest revealed dullness to percussion over the lower field of the left lung and coarse, moist rales above this area as well as in the base and axillary region of the right lung. The heart was enlarged to the anterior axillary line. A systolic thrill was palpated at the base where harsh systolic and diastolic murmurs were heard. The second sound was diminished at the aortic area and an apical systolic murmur was also noted. The cardiac rhythm was irregular. The liver was greatly enlarged to palpation but no other organs or masses were felt. There was 4-plus pitting edema of the ankles and legs.

Laboratory data showed a hemoglobin of 11 gm.; white cell count 9,000 per cu. mm. with a normal differential; erythrocyte sedimentation rate 35 mm. per hour; blood urea nitrogen 19 mg per cent; sodium, 122 mEq.; potassium, 5 mEq.; chloride, 96 mEq. Urinalysis was normal with specific gravity of 1.026. Roentgenogram of the chest revealed bilateral hilar congestion and a basal effusion of the left lung. Electrocardiogram showed atrial fibrillation and left ventricular preponderance. The sputum culture was reported as growing streptococci and non-hemolytic Staphylococcus aureus, while the urine culture showed vast numbers of Bacillus proteus.

The diagnosis on admission was rheumatic heart disease, with aortic stenosis and aortic and mitral insufficiency; atrial fibrillation, congestive heart failure, Class IV E, and probably bronchopneumonia.

COURSE IN THE HOSPITAL

The hospital course can be divided into three phases:

Phase I: January 29 to February 11, 1958. The patient was placed at bedrest with continuous oxygen therapy. She was given a low salt diet (0.5 gm. sodium chloride per day), mercurial diuretics and digoxin. The average fluid intake was 2,000 cc. per day. Her average output was about 1,000 cc. per day. The pleural effusion remained unchanged. The edema of the legs disappeared, but marked edema over the sacrum appeared. The patient became depressed, lethargic, anorexic and was frequently disoriented. A thoracentesis of 800 cc. of serous fluid was performed but the fluid rapidly reaccumulated. The clinical condition of her congestive heart failure did not change.

Phase II: February 11 to February 14, 1958. Because of the persistence of the apathy and disorientation, a "low salt syndrome" was suspected. The values for her serum electrolytes were as follows: sodium 89 mEq., chloride 70 mEq., potassium 4.6 mEq., and carbon dioxide 25 mEq., blood urea nitrogen 11 mg. per cent. The patient was given 3 gm. of sodium chloride daily for a total of 13 gm., and 500 mg. Diamox® daily. During this period of time, her clinical condition deteriorated. She was disoriented all the time, the edema became massive, and the patient appeared moribund. The total circulating plasma volume was calculated as 53 cc. per kilo (normal 40 cc. per kilo) by the radio chromium red cell method.

Phase III: February 14 to February 21, 1958. Sodium chloride therapy was discontinued. The dose of Diamox was increased to 750 mg. per day,

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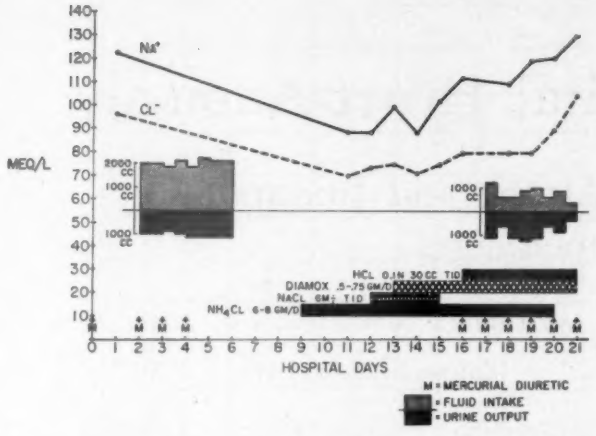


FIG. 1. Serum sodium and chloride values, fluid intake and output and summary of daily therapy.

ammonium chloride was given rectally and mercurial diuretics were administered daily. Fluid intake was restricted to an average amount of 600 cc. or less. The urinary output continued at about 1,000 cc. per day. On this regimen the patient gradually became clear-headed, the edema began to disappear and the serum electrolytes approached normal values (Fig. 1).

COMMENTS

This case is a good illustration of how the diagnosis of "low salt syndrome" was made improperly and consequently the patient was treated with sodium chloride. Actually, she was suffering from severe hemodilution secondary to the expansion of the extracellular fluid space from sodium and water retention due to congestive heart failure. When water and salt were restricted and an effort was made to raise her chloride levels, she mobilized her edema fluid, and restoration of electrolyte balance was effected. The urinary output became as great or greater than the intake of water. With this "drying out process" her electrolyte level returned to almost normal. This regimen, used so successfully by Rubin and Braveman[1,2] in the treatment of hyponatremia secondary to protracted failure, proved to be effective in this case.

Careful search of the literature indicates that this is the most extreme case of "low sodium" reported in congestive heart failure. The fact that the serum levels returned to almost normal during dehydration and diuresis indicates that a salt depletion "low salt syndrome" did not exist in this patient and that her body stores contained more than an adequate amount of sodium. The amount of sodium chloride administered was small and not sufficient to raise the serum sodium significantly; her condition deteriorated while receiving it. The differentiation of low salt syndromes has been well analyzed and discussed by Danowski.[3] More recently, Vogl[4] reviewed the subject with special reference to congestive heart failure and outlined the modes of management in a clear and concise fashion.

SUMMARY

Hyponatremia in congestive heart disease is discussed and the case of a patient with severe heart failure showing a serum sodium of 89 mEq. per L. is reported. This value returned to near normal levels with fluid restriction and diuresis. This case re-emphasizes that the "low salt syndrome" or hyponatremia of hemodilution is part of the clinical picture of congestive heart failure. Salt replacement is contraindicated. The serum sodium level returns to normal when vigorous treatment is directed to the heart failure and the mobilization of edema fluid. Administration of sodium chloride to correct the chemical "abnormality" may cause deterioration of the patient's condition.

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An Unusual Congenital Heart Anomaly

Tricuspid Atresia, Aortic Atresia and Juxtaposition of Atrial Appendages*

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An unusual congenital heart anomaly of the cyanotic type is reported, combining tricuspid atresia and aortic atresia with juxtaposition of the auricular appendages.

CASE REPORT

A twenty-seven year old woman delivered a full term female infant who showed spontaneous respirations and good color. There were no external congenital malformations.

This patient's three previous pregnancies resulted in normal deliveries with children who are apparently in good health. It is reported that during the first trimester of her last pregnancy all the children acquired rubella.

During the first twenty-four hours, increasing cyanosis developed progressively with dusky color and labored respirations. The cyanosis involved both the lips and nailbeds. The respirations progressively increased in rate (up to 112) and a grade 2 systolic murmur was heard in the lower left axillary region. The second sound was narrowly split and maximal over the lower left sternal border.

The x-ray film of the chest demonstrated marked generalized cardiac enlargement (Fig. 1). The electrocardiogram showed a rate of 160 with a normal sinus rhythm. There were tall R waves in the right-sided precordial leads, suggesting right ventricular preponderance (Fig. 2). The infant's condition deteriorated, terminating in death within fifty-three hours after birth.

POSTMORTEM EXAMINATION

The positive findings were confined to the mediastinum. The heart with the aortic arch weighed 23 gm. When viewed *in situ*, it displayed a round shape with a somewhat straight right border. Its transverse diameter was 4.5 cm.

Aorta: The aorta seemed to arise from the upper edge of the right border as a thin, slender tube, exhibiting an exceedingly narrow lumen (Fig. 3). When opened, the lumen displayed a bulbous dilatation at its origin which was arising from a blind point in the ventricular wall. The cusps of the aortic valve consisted of thin invaginations of the aortic intima (Fig. 4). At this point, the diameter of the wall of the aorta measured up to 0.5 cm. whereas the portion distal to it and up to the point of the innominate artery became much narrower, not exceeding 0.2 cm. in diameter. Thereafter, it became wider until the point of insertion of the ductus arteriosus where it attained a caliber of 0.6 cm. (Fig. 3). The orifices of the coronary arteries arose from the wall of the ascending aorta 0.3 cm. distal to the base of the bulb-like dilated portion of the lumen with the os of the right coronary artery lying slightly higher.

Atria: The right atrial appendage appeared con-

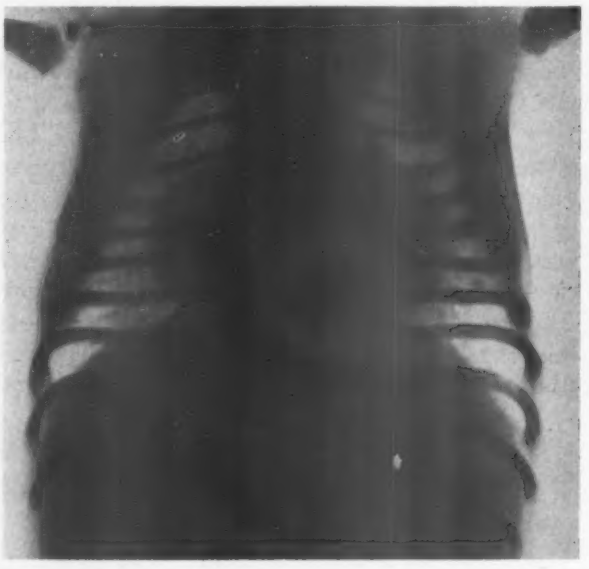


FIG. 1. *Roentgenogram in anteroposterior view.* Marked enlargement of the heart with dilatation of the right auricular appendage gives a balloon appearance occupying a large portion of the thorax. Note the accompanying marked pulmonary congestion.

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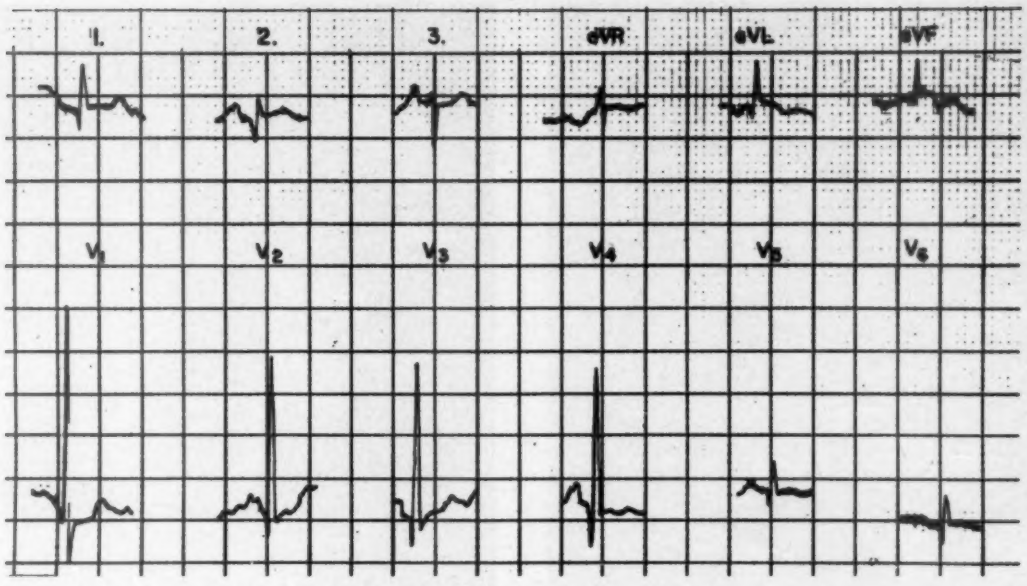


FIG. 2. *Electrocardiogram.* The record is suggestive of right ventricular preponderance, as indicated by the tall R waves in the right-sided precordial leads.



FIG. 3. *Anterior view of the heart.* The right atrial appendage (R.A.) is to the left of the pulmonary artery and beside the left atrial appendage (L.A.) which is seen in the outer right of the picture overlying part of the ventricle. The aorta (A) is very narrow in the first part (0.1 cm.) and is seen originating from the upper right external border of the ventricle from a wider but blind portion which represents a primitive left ventricle.



FIG. 4. *Close view of the first part of the opened aorta.* The intimal invaginations, representing primordial aortic valves, are visualized. The ostium of the right coronary artery can be seen arising from the aortic wall and slightly above the mentioned valve.

gested, dilated and lay to the left of the pulmonary artery between it and the left atrial appendage (Fig. 3). When collapsed, the right and left atrial appendages measured in transverse diameter 2 cm. and 1 cm., respectively. The right atrium lay posterior to the pulmonary artery and revealed no tricuspid orifice.

Tricuspid Valve: At the expected site of the tricuspid valve on the floor of the right atrium, a thin, small fibrous strand was found, beneath which a



FIG. 5. *Superior close view of the right auricle.* The tricuspid valve (T.V.) is atretic. The coronary sinus (C.S.) is normally present. The inferior vena cava (I.V.C.) has been opened in order that the atrium will be revealed more easily. Chiari's network (C.N.) connects the two opposite walls of the atrium.

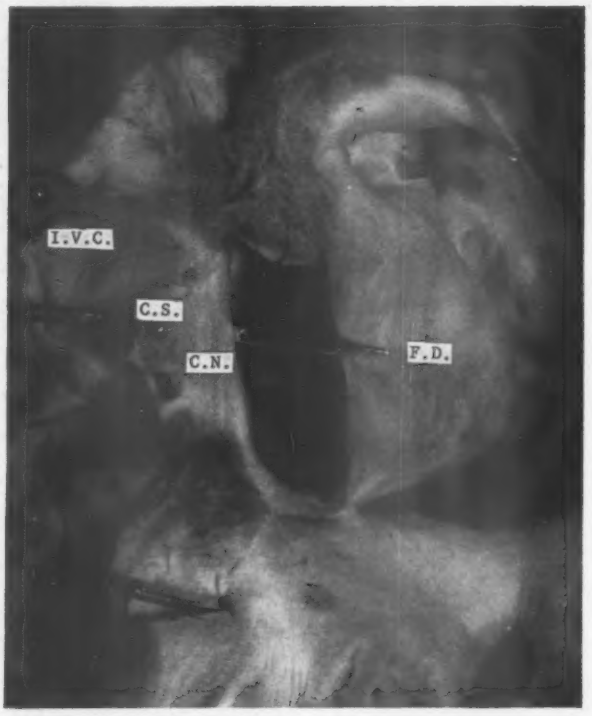


FIG. 6. *Another view of the foramen ovale (F.O.), bulging into the left atrium.* The probe shows the outflow of the blood stream through the Chiari's band and foramen ovale.

shallow dimpling of the wall appeared to represent the atrioventricular septum. No tricuspid orifice could be demonstrated. The venae cavae and the coronary sinus were present (Fig. 5). The only outlet from the right atrium appeared to be a widely patent foramen ovale partly blocked by a saccular, aneurysmal fossa ovalis bulging into the left auricle. Slightly to the right of this interatrial septum and parallel to its free upper margin, there was a fenestrated fibrous band attached to the opposite side of the right atrium (Fig. 6). The four pulmonary veins entered the left atrium.

Ventricles: The mitral valve divided the left atrium from a single, enlarged ventricle, exhibiting a markedly hypertrophied myocardium measuring up to 0.9 cm. in thickness. The pulmonary conus and pulmonary artery were quite large, up to 0.9 cm. in diameter, and appeared to carry the cardiac outflow towards a patent ductus arteriosus. This was attached at the junction of the aortic arch and descending aorta (Fig. 7).

COMMENTS

In interpreting the anatomical findings, it is suggested that in the left atrium there was a mixture of venous and arterial blood coming from the pulmonary veins and right atrium.

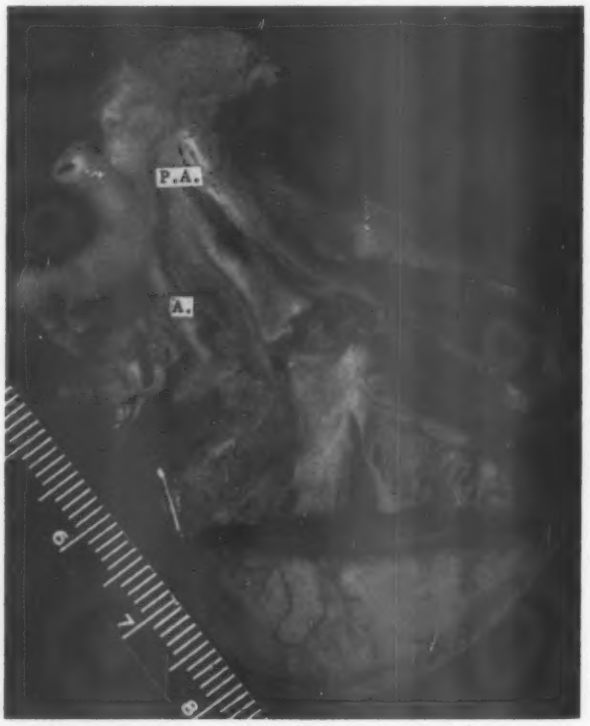


FIG. 7. *Anterior view of the opened heart.* There is a single ventricle with a markedly hypertrophied wall. The pulmonary conus and artery are disproportionally dilated (0.9 cm.). There is a wider patent ductus arteriosus (P.A.).

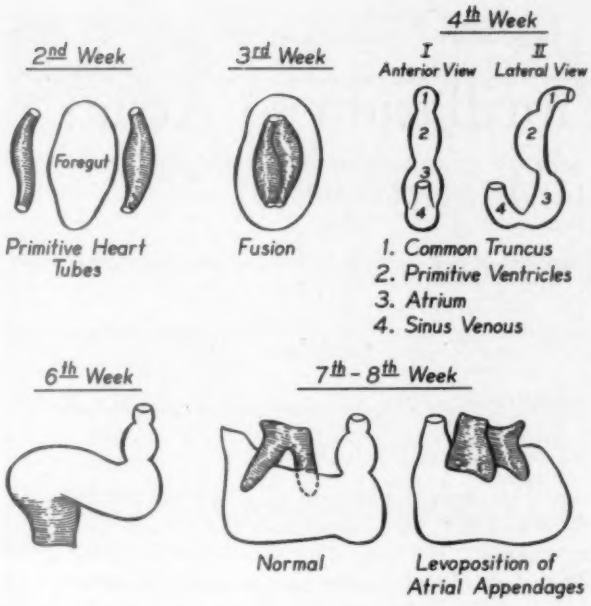


FIG. 8. *Embryonic development of the heart.* This illustration shows the failure of the atrium to expand normally at the seventh to eighth week of the embryonic life, and both auricular appendages overriding the upper border of the heart to the left of the common truncus.

This increased its volume to almost double its capacity with resultant pulmonary congestion and increased outflow through the mitral orifice into a single ventricle. The left ventricle and aortic valve were hypoplastic and had never functioned due to their lack of communication with the right or single ventricle. This resulted in a rudimentary left ventricle with primordial aortic cusps of a six- to seven-week embryo.[1]

The division of the truncus arteriosus at an abnormal level of the embryonic common trunk lying much to the right of the midline seems to be the cause of the narrow lumen of the ascending aorta and the dilated pulmonary truncus, with a resulting hypoplastic, non-functioning left ventricle. Transposition of the right atrial appendage to the left of the pulmonary artery has been reported in sixteen other cases and has been called "levoposition" or "juxtaposition."[2] It is due to failure of the single atrium to expand laterally when it is constricted between the gut and bulbus (Fig. 8). This probably is due to a simultaneous abnormal division of the bulbus[1] with the gradual increase in size of the right ventricle and pulmonary artery. Furthermore, the rapidly expanding right atrium may cause the levoposition of the atrial appendage, as an inevitable mechanical outlet. A preceding cephalic shift of the atrium might have been an additional predisposing factor.

The fibrous interanastomosing strands found in the right atrium assume no pathological significance and have been reported as an incidental finding under the name of "Chiari's network."[3]

SUMMARY

In a newborn female infant an unusual congenital heart anomaly was observed with no typical physical or laboratory signs that would justify a diagnosis of the usual patterns. The life of the infant extended only two days, and an autopsy was carried out. Tricuspid atresia, aortic atresia and juxtaposition of the auricular appendages were the major postmortem findings. The pathophysiology and embryology of the case are also briefly discussed.

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Conversion of Atrial Fibrillation to Atrial Flutter As a Manifestation of Digitalis Toxicity*

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DIGITALIS toxicity may cause a variety of cardiac arrhythmias, the most frequent of which are ventricular in origin. Coupled ventricular beats (bigeminal rhythm) are especially common with digitalis overdosage and ventricular tachycardia may ultimately ensue. Less common manifestations of digitalis toxicity are the atrial arrhythmias of which atrial tachycardia with block is the most characteristic. Atrial flutter and atrial fibrillation are considerably less frequent.

Sixteen cases of atrial flutter secondary to digitalis toxicity have been reported.[1] In most instances the atrial flutter was preceded by a normal sinus rhythm. A much less frequent sequence is the conversion of atrial fibrillation to atrial flutter as a manifestation of digitalis overdosage. It is the purpose of this report to describe such an instance and to discuss the possible mechanisms involved.

CASE REPORT

J. B., a thirty-two year old white woman, had a mitral commissurotomy performed for rheumatic mitral stenosis six months prior to admission. - though temporarily improved, dyspnea, fatigue, chest pain and edema of the ankles subsequently recurred. Her cardiac rhythm during this interval was atrial fibrillation (Fig. 1). One week prior to admission she had increasing nausea and vomiting, and the digitalis which she had been receiving daily was discontinued.

Physical examination revealed a chronically ill, white woman who appeared severely dyspneic. Distention of the neck veins was prominent bilaterally. Examination of the lungs revealed marked dullness to percussion over the lower lobe of the right lung and absence of breath sounds in the same area. The heart rate was 120 per minute, and the rhythm was regular. A loud blowing systolic apical murmur was well transmitted to the left axilla, and a rumbling diastolic apical murmur was also heard. The mitral first sound was normal; the pulmonic second sound was accentuated. The liver edge was palpable at the level of the umbilicus. One-plus peripheral edema was present bilaterally.

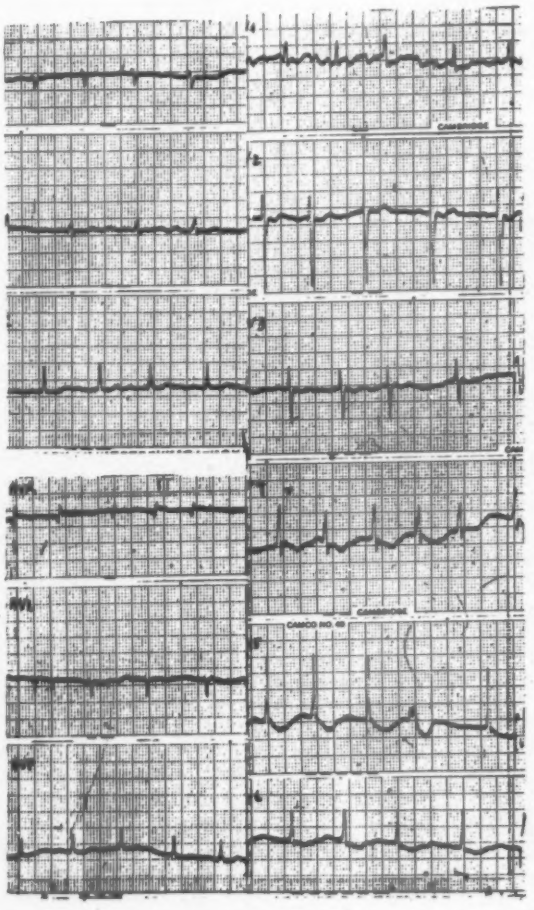


FIG. 1. The basic cardiac rhythm in this patient after surgery was atrial fibrillation.

* From the Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania.

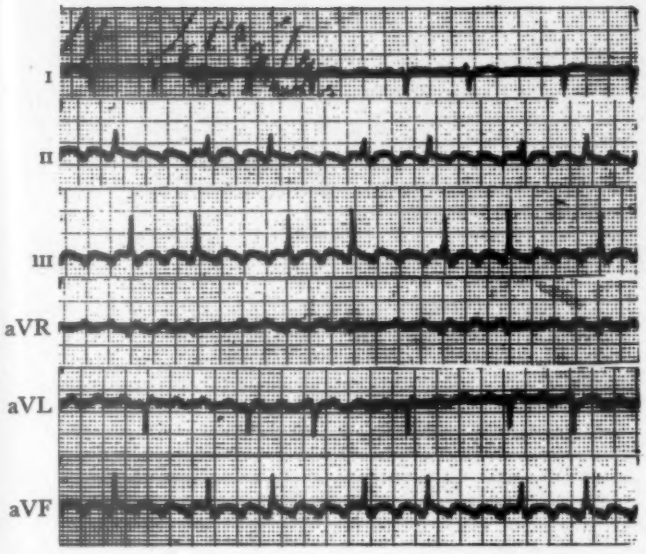


FIG. 2. Atrial flutter with partial heart block and Wenckebach phenomenon caused a pseudobigeminal rhythm.

The electrocardiogram taken on admission revealed atrial flutter with a 2: 1 A-V block; the atrial rate was 240 per minute. The chest roentgenogram confirmed the presence of a right pleural effusion and pulmonary vascular congestion. Serum sodium was 141 mEq./L.; potassium 5.3 mEq./L.; carbon dioxide 18.2 mEq./L.; and chlorides 88 mEq./L.

Treatment: The administration of digitalis was withheld for four days because of suspected digitalis toxicity. However, the atrial flutter with 2: 1 block persisted and it was decided to redigitalize the patient with Cedilanid® because of the rapid ventricular rate. On the fifth hospital day, the electrocardiogram revealed atrial flutter with varying degrees of block (Fig. 2), and the patient had increasing nausea and vomiting. On the seventh hospital day, potassium chloride (2 gm. administered four times a day) was given orally. The atrial flutter continued and on the following day 40 mEq. potassium chloride in 5 per cent glucose solution was infused intravenously over a four-hour period. During the infusion the atrial flutter converted to atrial fibrillation; the nausea and vomiting disappeared entirely during the subsequent twenty-four hours. Thereafter the patient was treated with oral potassium. On the twelfth hospital day digoxin therapy was begun (0.25 mg. given daily) and the atrial fibrillation continued with a well controlled ventricular rate.

COMMENTS

Although atrial tachycardia with block is a not infrequent manifestation of digitalis toxicity, paroxysmal atrial flutter due to digitalis overdosage is quite uncommon. Currently it is believed that atrial tachycardia is most probably caused by the discharge of repetitive impulses from a single ectopic atrial focus. If we assume the latter theory to be correct, then an acceleration of this ectopic discharge could result in atrial flutter. Paroxysmal atrial tachycardia with block actually appears to be a hybrid form of atrial tachycardia and atrial flutter in which the atrial rate has progressed to a speed at which physiologic atrioventricular block must supervene. At present there is no adequate explanation why atrial flutter should be a less common manifestation of digitalis toxicity than atrial tachycardia.

Mechanisms of Atrial Flutter Due to Digitalis Toxicity: It is not difficult to conceive the initiation of an ectopic atrial pacemaker due to digitalis with the subsequent conversion of normal sinus rhythm to atrial tachycardia or even atrial flutter. However it is much harder to account for the conversion of atrial fibrillation to atrial flutter as a manifestation of digitalis toxicity. Nevertheless, there are two possible mechanisms which could explain the latter sequence of events. First, it is conceivable that large doses of digitalis (with its known myocardial depressant action) may cause a slowing of the ectopic atrial discharge with the subsequent conversion of atrial fibrillation to atrial flutter. Also, it is possible that the digitalis might convert the atrial fibrillation to normal sinus rhythm and that a new ectopic atrial focus might subsequently become established with the continued use of the drug.

Although neither of these two explanations has been established, there are certain clinical findings which are consistent with the latter presumption. Lown and Levine[2] described fifteen patients with paroxysmal atrial tachycardia with block due to digitalis toxicity in whom atrial fibrillation had been the previously established cardiac rhythm. In each instance in which the original rhythm was re-established with the use of potassium salts or procaine amide, a temporary normal sinus rhythm resulted prior to the reappearance of the atrial fibrillation. The normal sinus rhythm which temporarily supervened sometimes persisted for a day or even two; and it is of interest that the temporary conversion from atrial tachycardia with block to normal sinus rhythm and, ultimately, atrial fibrillation was occasionally observed in patients with advanced cardiac decompensation, huge hearts, and even long standing atrial fibrillation.

Criteria for Attributing Atrial Flutter to Digitalis Toxicity: According to Coffman,[1] authentic cases of atrial flutter due to digitalis should

meet the following criteria: (1) the arrhythmia should develop while the patient is taking digitalis; (2) the patient should not be taking any other drug known to cause cardiac arrhythmias; and (3) the abnormal rhythm should disappear when the ingestion of digitalis is discontinued. The present case satisfies these criteria; and, in addition, the conversion was obviously facilitated by the intravenous administration of potassium. Finally, the presence of Wenckebach phenomenon observed during the period of atrial flutter further suggests digitalis toxicity as the offending mechanism in the present case.

Summary

A patient in whom atrial fibrillation was converted to atrial flutter as a manifestation of digitalis toxicity is described. The withdrawal of digitalis and the intravenous administration of potassium facilitated the re-establishment of the original rhythm.

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Patent Ductus Arteriosus in a Patient Surviving to Seventy-Four Years*

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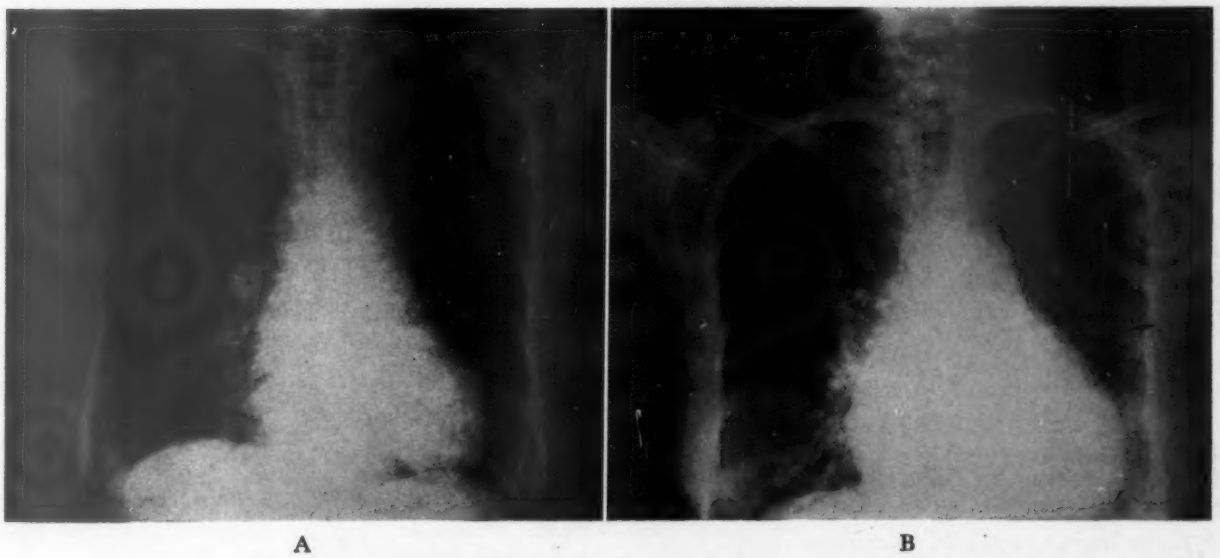
CHAVEZ et al.,[1] in a review of over 28,000 reports on cardiac patients, including 200 with patent ductus arteriosus, found none over fifty-five years of age and only one over fifty. This is in agreement with other reports alleging the rarity of this anomaly in the aged.[2–4] In the case to be reported, a diagnosis of patent ductus was made in a seventy-one year old woman who lived to her seventy-fifth year, at which time the clinical impression was confirmed at necropsy.

CASE REPORT

The patient had been known to have a cardiac condition since she was three years old, when she allegedly received her first dose of digitalis. She had never been cyanotic, edematous or severely decompensated, except for mild left ventricular failure in recent years which had been controlled by the administration of digitalis.

Physical examination showed a seventy-one year old, well developed, white woman in no distress. Her respiratory rate was 22 per minute and her blood pressure 180/80 mm. Hg. There was grade 1 sclerosis of the retinal arterioles and absent dorsalis pedis and posterior tibial pulses; the remaining peripheral pulses were equal and palpable. There was bilateral palmar erythema. Rales were limited to the posterior base of the right lung, the remainder of the lung fields being clear.

There was a regular sinus rhythm with occasional premature contractions. The point of maximal apical impulse was in the fifth left intercostal space, just beyond the mid-clavicular line. A harsh systolic murmur was heard at the base, equally at the pulmonic and aortic areas, with a well preserved second aortic sound. There was a late systolic accentuation of this murmur, which was continuous with a diastolic murmur at the base associated with a snapping second pulmonic sound. The systolic and diastolic murmurs were of greatest intensity at the pulmonic area, although the systolic component was transmitted down the left sternal border to the mitral area. There was no thrill and no presystolic apical murmur.



A B

FIG. 1. Roentgenograms of the chest. A, February 25, 1954. B, October 25, 1956.

* From Princeton Hospital, Princeton, New Jersey.

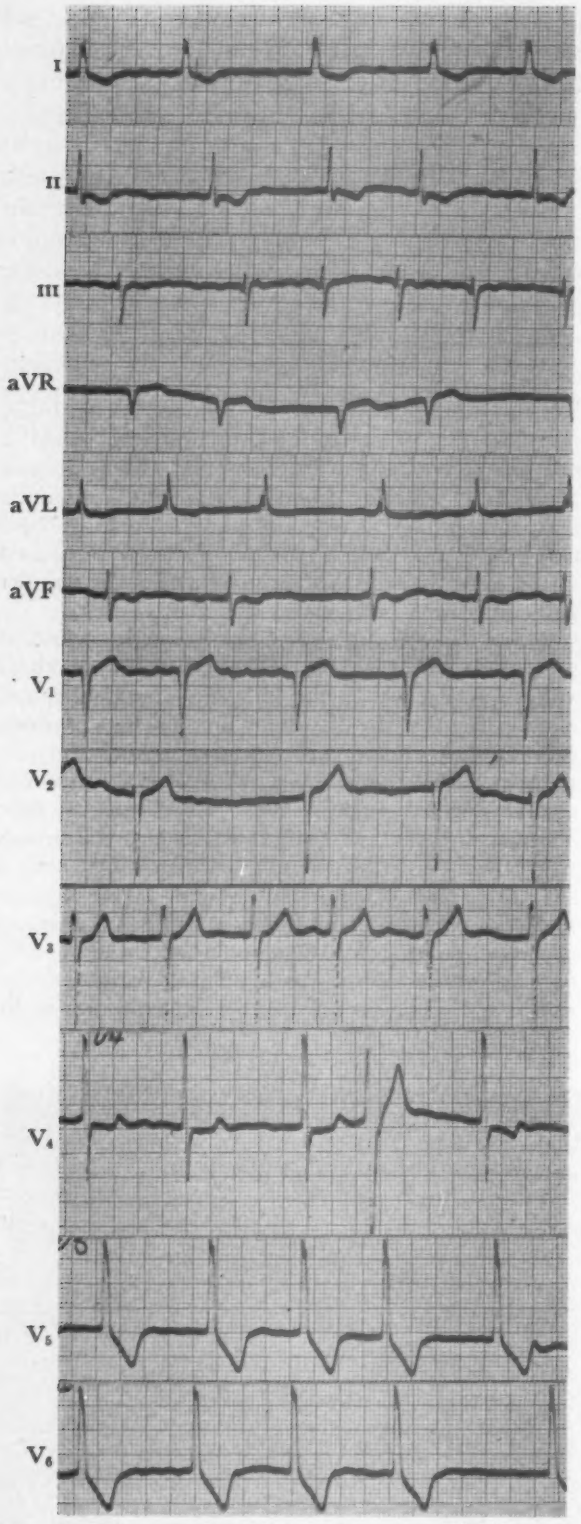


FIG. 2. Electrocardiogram taken on December 1956, showing auricular fibrillation with evidence of left ventricular hypertrophy and digitalis effect.

There was a leukopenia of 2,600 to 3,800, with a normal differential while she was receiving quinidine; when administration of the drug was discontinued, her white blood count rose. The *chest roentgenogram*



FIG. 3. View of base of heart showing right ventricle and open pulmonary artery. Descending limb of aortic arch is laid back over heart to show applicator stick through ductus arteriosus with aortic and pulmonary openings.

(Fig. 1) revealed a calcified aortic arch with fullness at the pulmonary artery segment, a slightly enlarged left ventricle and increased pulmonary markings. The *electrocardiogram* demonstrated a regular sinus rhythm with an occasional premature nodal contraction. There were large, broad P waves, particularly in leads II and III, and changes in the ventricular deflections suggesting left ventricular hypertrophy with digitalis effect. A later record showed auricular fibrillation (Fig. 2).

Following this examination, the patient was readmitted to the Princeton Hospital for treatment of congestive heart failure and an infection of the upper respiratory tract. Her terminal episode took place on February 15, 1957, when she was admitted with severe abdominal pain followed by intestinal obstruction; this was complicated by congestive heart failure and resulted in her death at the age of seventy-four.

AUTOPSY REPORT*

Respiratory System: Bilateral soft pleural adhesions were found involving the lower lobes laterally and posteriorly. The major bronchi were filled with a frothy exudate. The left lung weighed 550 gm., the right lung 660 gm. Both lungs were heavy with fluid. *Microscopic Diagnosis:* Chronic congestion and pulmonary edema. There were alternating patches of dilated and collapsed alveoli; many alveoli

* Autopsy performed by Dr. Margaret Collins.

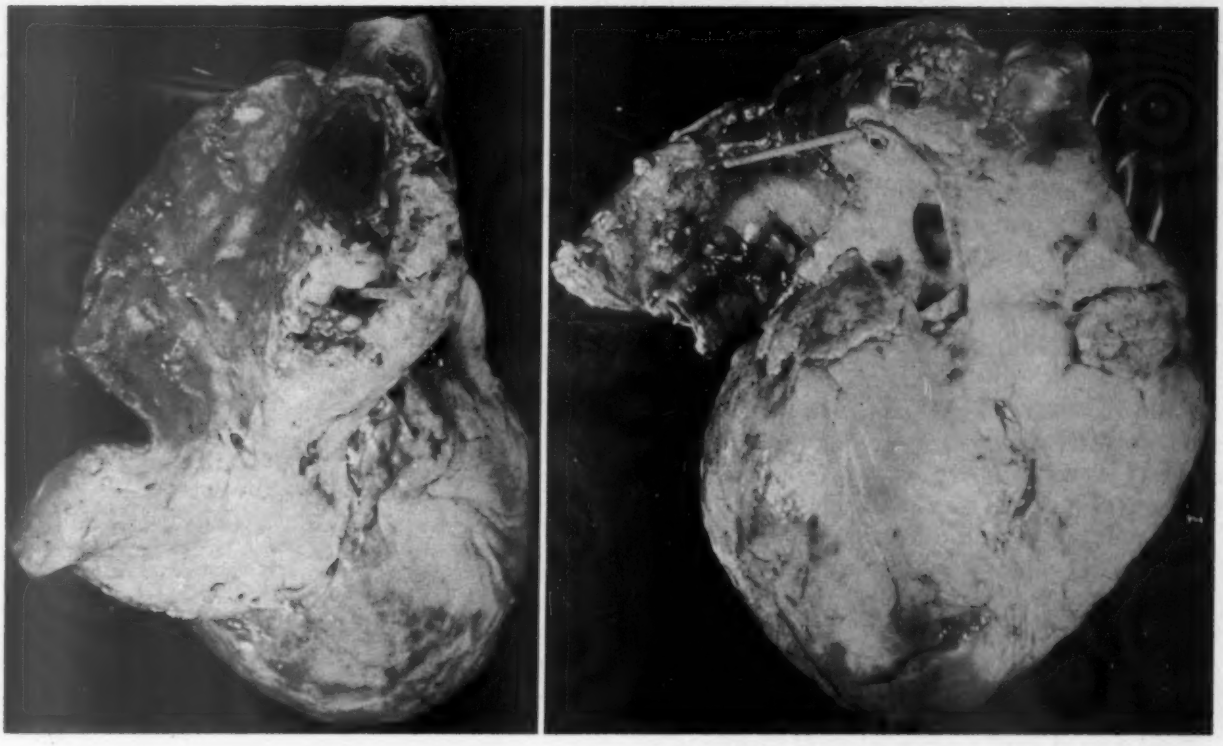


FIG. 4. (Left) Descending limb of aortic arch viewed from above. Applicator stick is in opening of ductus arteriosus. Note calcific sclerotic plaque around aortic opening.

FIG. 5. (Right) View of left border of heart with pulmonary artery opened longitudinally. Applicator stick is in pulmonary opening of ductus arteriosus.

contained hemosiderin-filled phagocytes. The medium-sized and small arteries in some instances showed thickenings of the walls by intimal fibrous tissue proliferation. Most of the vessels showed no change.

Cardiovascular System: The pericardial space was obliterated by fusion of the visceral and parietal pericardium. The *heart* weighed 630 gm. Coronal sections showed a marked concentric hypertrophy of the left ventricle with the wall measuring 2.5 cm. in thickness. A small area of scarring was found at the posterolateral angle of the left ventricle on the endocardial wall. This lesion was located 3 cm. above the apex of the heart. The mitral valve showed fusion of the leaflets and a nodular, calcified lesion on the atrial surface. The ventricular surface showed a rigid calcified shelf with the tips of the valve leaflets turned under. Both coronary arteries showed calcified walls. The circumflex branch of the left coronary showed a reduction in the diameter of the lumen. *Microscopic Diagnosis*: Focal myosclerosis and myonecrosis; myocardial hypertrophy.

The *aorta* showed advanced ulcerative atherosclerosis throughout its length. The ductus arteriosus was present and patent (Figures 3, 4 and 5). The aortic ostium showed sclerosis and nodular calcification with partial obstruction of the lumen. The pulmonary ostium was free of sclerotic change and had a lumen diameter of 0.5 cm. The ostia of all the aortic branches showed marked proliferative atherosclerotic changes. There was a partially organized thrombus in the aortic lumen just below the diaphragm. This thrombus involved the ostia of the celiac and superior mesenteric arteries and extended to, but did not occlude, the renal arteries. The primary branches of the celiac artery showed medial sclerosis with marked reduction in the lumen. The portal vein was patent and free of thrombi. The renal arteries showed sclerotic change limited to the first centimeter of their length.

Gastrointestinal System: The stomach was markedly dilated and showed patchy areas of hemorrhagic necrosis of the mucosa. The intestinal tract throughout its length was frankly gangrenous. The *liver* weighed 1,210 gm. The surface showed large, irregular, patchy areas of a subcapsular hemorrhage. The cut section was dusky and cyanotic. *Microscopic diagnosis:* Acute diffuse edema; portal fibrosis. The *spleen* weighed 210 gm. Section revealed a large area of recent infarction in each pole with an area of relatively normal spleen between. The *pancreas* was normal on both gross and microscopic examination. The *mesentery* was free of thrombi and the cut peripheral vessels showed stasis of blood.

Conclusions: It was concluded that this patient had a persistent, functioning patent ductus arteriosus,

associated with arteriosclerotic heart disease. Her terminal events were those of intermittent mesenteric ischemia resulting in a gangrenous bowel.

Comments

Since the report of two such cases in 1951[2] (one confirmed at autopsy), no others have been reported, attesting to the rarity of this lesion in this age group. However, it must be considered that this defect may be overlooked in routine autopsy procedures.

It is open to speculation whether surgery would have altered this patient's prognosis had the correct diagnosis been made in the past twenty years. There is no question of the success of surgical correction in improving the prognosis of patent ductus in children and young adults.[5] Is there an age group that would not benefit by cardiac surgery? Perhaps such a group does exist and could simply be treated with prophylaxis against subacute bacterial endocarditis. Cosh[6] reports follow-up into adulthood of unligated subjects attesting to "the general well-being of the adult patients, the occurrence of pregnancies and childbirths (twenty-three times) without complication," and even "occasional apparent spontaneous closure of the ductus in early adult life." He concluded that the asymptomatic adults need not undergo surgery provided that care is taken to prevent bacterial endocarditis.

Thus, this question can only be answered by the careful reporting of all cases and the careful analysis of such data as exact clinical and laboratory status and exact causes of death. Once normal growth and development have occurred, the remaining purpose of ligation is the prevention of bacterial endocarditis and cardiac decompensation. This case and the others referred to[6] may prove that it is more than academic to ascertain physiologic measurements in adults with patent ductus in deciding on the possible benefit from surgery.

Summary

A case of persistent patent ductus arteriosus in a seventy-four year old woman in whom the clinical diagnosis was confirmed at autopsy is reported.

Acknowledgment

Kind acknowledgment is expressed for the sincere cooperative efforts of Drs. Benedict Scasserra, Margaret Collins and Thomas Harvey.

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Congenital Absence of the Aortic Arch Associated with Patent Ductus Arteriosus and Ventricular Septal Defect*

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ALTHOUGH congenital absence of the aortic arch has been recorded less than thirty times in the world literature, there has been an apparent increase in the frequency with which this defect has been recognized in recent years. This anomaly has reportedly never been diagnosed accurately without thoracotomy or, more frequently, autopsy. In view of the potential reparability of the defect, it is considered worthwhile to report the following case which points out the need for complete diagnostic studies in infants with suspected congenital cardiac disease.

CASE REPORT

S. L. K., an eleven week old white female infant, was admitted to the hospital on October 19, 1959. A cardiac murmur had been discovered by the family physician directly after birth. Otherwise, the baby seemed to be perfectly well for the first two months of life, although she failed to gain in weight or size. Five days prior to admission, there was a rise in temperature and the infant was treated with penicillin. Two days later, a local physician diagnosed pneumonia and cardiac failure. At this point digitalization was carried out with digoxin. Because the infant's condition did not seem to improve, she was transferred to this center.

Past history revealed that the mother's pregnancy had been complicated throughout by moderate to severe vomiting as well as by a fall downstairs during the second month of gestation. During the fifth month of pregnancy, an undiagnosed illness occurred which was characterized by fever only.

The infant weighed 5 pounds and 15 ounces at birth; a normal spontaneous delivery was effected after five hours of labor. Following delivery, the baby had been placed in an incubator for five days "because of a feeding problem." According to the mother, the baby had always eaten normally, although she weighed only 7 pounds and 4 ounces at ten weeks of age. Cyanosis had never been noted, not even when the baby was crying or straining. Motor development seemed adequate; the baby was active and able to hold her head up; she reacted to stimuli and smiled easily.

Physical Examination. The infant's weight, length and head circumference were below the third percentile for her age group. Her temperature was 101°F., pulse 150, respirations 30 and blood pressure, 110/0 mm. Hg in the arm by cuff method. By flush method, blood pressure was 90 mm. Hg systolic. No definite cyanosis was present, but the patient's skin was definitely pallid and had a decided grayish cast. Positive physical findings included moist, inspiratory rales at bases of both lungs posteriorly. A grade 4 pansystolic murmur was heard over the entire precordium with maximal intensity in the fourth left intercostal space and toward the apex. The murmur was of medium pitch and had a blowing character. There was an associated thrill over the lower left side of the precordium. The second cardiac sound over the pulmonic area was accentuated. The liver edge was palpable 2 cm. below the right costal margin.

Laboratory Data: The hemoglobin was 13.6 gm., white blood cells 23,000 with 58 per cent polymorphonuclears, 3 per cent stabforms and thirty-two lymphocytes. Urinalysis on admission showed a 1-plus proteinuria.

X-ray examination on admission showed the heart to be markedly enlarged (Fig. 1) with right ventricular and probably left ventricular hypertrophy present. Pulmonary vasculature was markedly engorged. On fluoroscopy and lateral and oblique chest films, there was questionable left atrial enlargement.

The electrocardiogram was interpreted as showing right ventricular hypertrophy, digitalis effect and large, peaked P waves in leads I, II, aVF and V_6.

Course: The clinical diagnoses at the time of admission to the hospital were ventricular septal

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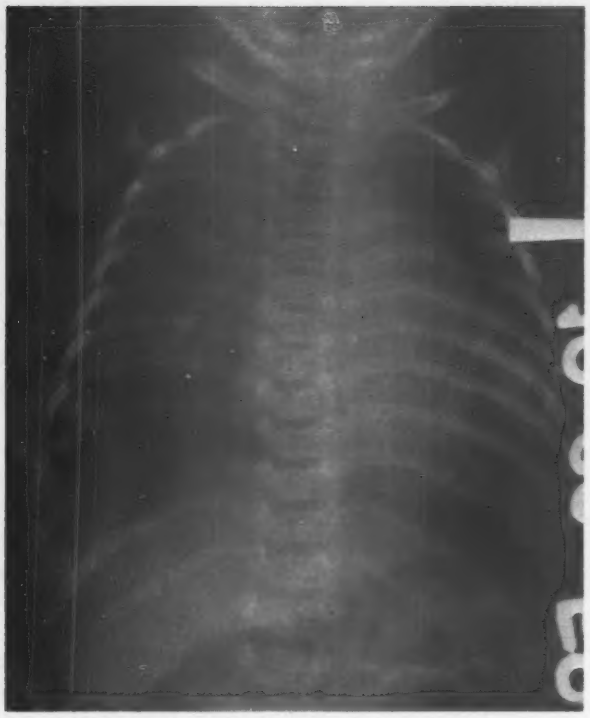


FIG. 1. Posteroanterior roentgenogram taken on day of admission to hospital shows marked cardiac enlargement and congested lung fields.

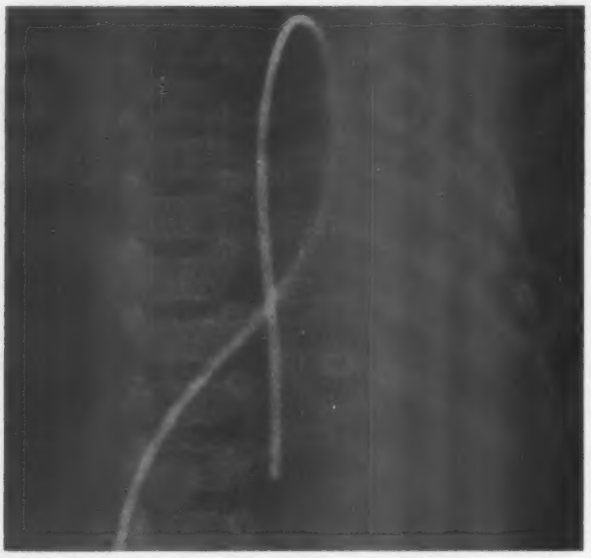


FIG. 2. Spot film taken during right heart catheterization. Catheter passage through patent ductus and into descending thoracic aorta is demonstrated.

defect and/or patent ductus arteriosus complicated by congestive cardiac failure. Digitalis therapy was actively pursued and Chloromycetin was instituted to combat any possible pneumonitis. The patient's temperature fell to normal levels on the night of admission. She was taking her formula well and sleeping normally. Over the next few days, repeated examinations failed to disclose any overt cyanosis, although the skin color remained pallid. Cardiac catheterization was performed nine days following admission after adequate digitalization had been achieved.

Cardiac Catheterization: A No. 5 cardiac catheter was introduced without difficulty through a left saphenous vein. The right atrium, right ventricle and main pulmonary artery were entered without difficulty. A left superior vena cava was entered from the right atrium. In addition, the catheter passed across a patent ductus arteriosus on numerous occasions and entered the descending thoracic aorta (Fig. 2), easily reaching a level well below the diaphragm. Blood samples from the aorta, the area of the ductus, the main pulmonary artery and the outflow tract of the right ventricle all showed oxygen saturations which were practically identical. Numerous samples taken in the right ventricle were also indicative of a left-to-right shunt at the ventricular level.

Pressure recordings revealed a moderate right ventricular hypertension of 50/2 mm. Hg, the systolic pressure being identical in the main pulmonary artery. Pressure in the right atrium was normal. On repeated passage of the catheter through the patent ductus arteriosus, pressure tracings were obtained from the aorta in the range of 33/19 mm. Hg. It was believed at the time that these curves actually represented damping of a normal arterial tracing due to the acute angling of the catheter during its passage through the ductus.

Further analysis of blood samples from the aorta revealed only 93 per cent oxyhemoglobin saturation despite the fact that the patient was receiving an anesthesia mixture of Fluothane® in 100 per cent oxygen. This seemed to indicate that there was, at least during the catheterization procedure, shunting of blood from right to left, either at the level of the ductus or through a ventricular septal defect.

Diagnoses following catheterization were ventricular septal defect and patent ductus arteriosus with right-to-left shunting through either the ventricular defect or the ductus. In view of the catheter passage through a patent ductus, angiocardiography was not thought to be needed or indicated.

Course Following Catheterization: Although catheterization was well tolerated, twenty-eight hours after the procedure the patient's temperature suddenly rose to 102°F. and respirations became labored. A white blood count at this point showed 19,300 white cells per cu. mm. with 49 per cent polymorphonuclears and 51 per cent lymphocytes. A chest film taken on the evening of the temperature spike showed little, if any, over-all change in the appearance of the lungs since the original chest film. No specific zone of pneumonic infiltration could be outlined. Blood cultures drawn at the same time were negative.

The following morning respirations had increased



FIG. 3A. Autopsy specimen demonstrating absence of the aortic arch. MPA = main pulmonary artery. PDA = patent ductus arteriosus. AA = ascending aorta. DA = descending aorta. SA = subclavian arteries.

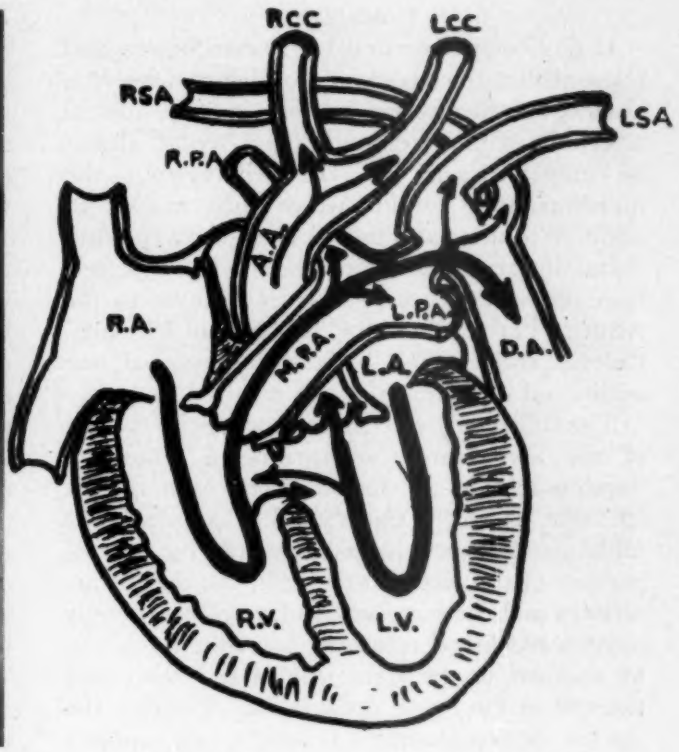


FIG. 3B. Diagrammatic representation of hemodynamics. R.V. = right ventricle. L.V. = left ventricle. R.A. = right atrium. L.A. = left atrium. M.P.A. = main pulmonary artery. L.P.A. = left pulmonary artery. R.P.A. = right pulmonary artery. R.S.A. = right subclavian artery. L.S.A. = left subclavian artery. R.C.C. = right common carotid. L.C.C. = left common carotid. A.A. = ascending aorta. D.A. = descending aorta.

to 72 per minute and were of a gasping character. There was frank cyanosis. The patient was placed in a croupette with oxygen therapy. The temperature steadily increased to over 105°F. despite antibiotic therapy and nineteen hours after the onset of fever the patient died in extreme respiratory distress.

Autopsy Findings: The heart weighed 53 gm. (normal for the patient's body weight: 15 to 20 gm.). There was dilatation of all cardiac chambers, especially the right ventricle. An exceptionally large main pulmonary artery originated in the right ventricle and gave rise to the right and left pulmonary arteries. A large patent ductus arteriosus connected the pulmonary artery with the descending thoracic aorta (Fig. 3A). The right and left subclavian arteries originated in the first part of the descending aorta.

A small, hypoplastic aorta arose from the left ventricle directly over a high interventricular septal defect measuring 0.75 cm. in diameter (Fig. 4). This vessel terminated as the right and left common carotid arteries. Also noted was a left superior vena cava emptying into the right atrium. There was gross pulmonary congestion and edema with intra-alveolar hemorrhage and petechiae. The liver was moderately enlarged, weighing 100 gm.



FIG. 4. Large, high interventricular septal defect indicated by probe at autopsy.

Comments

It has been suggested by Everts-Suarez and Carson[1] that the association of defects involving absence of the aortic isthmus, patent ductus arteriosus and interventricular septal defect be considered a trilogy. In their review of the literature they found twelve such cases. In addition to these and their own case, seven additional instances of association of these defects have reportedly[3] been found by Manion in the Armed Forces Institute of Pathology files. Celoria and Patton[2] have since reported one additional occurrence of the triad.

The embryologic aberration producing atresia of the aortic arch, comprising a failure of development of the fourth aortic arch on the left side, is easily understood. Circulation is maintained through patency of the dorsal portion of the sixth aortic arch, the ductus arteriosus and the interventricular defect whereby oxygenated blood returning from the lungs can be shunted to the right side of the heart and thereby to the lower body parts. If either the ductus or septal defect is absent, the subject cannot usually live for more than a few hours or days. Cases similar to our own have been reported in which the patient survived to the age of five years.[3] In such instances extensive collateral circulation has been seen to develop between the two portions of the aorta. Celoria's embryologic review[2] provides an excellent picture of the various types of atresia encountered. We have not, however, been able to find a reported case which incorporates the unusual origins of carotid and subclavian arteries seen in our patient.

In our case there was little clinical evidence to suggest or establish the correct diagnosis. Cyanosis was not obvious, either in a generalized form or in unilateral distribution as has been reported. Failure to develop normally, hepatomegaly and other signs of congenital cardiac disease with decompensation were of a nonspecific nature. The cardiac murmur itself was also non-characteristic of any particular lesion, although it strongly suggested the presence of a ventricular septal defect. The routine chest roentgenograms and electrocardiogram did not help to suggest that such an unusual anomaly was present.

Merrill, Webster and Samson,[4] in their reported case in which the patient was subjected to cardiac catheterization, suspected a patent ductus with right-to-left shunting and an incomplete form of pre-ductal aortic coarctation. Dorney, Fowler and Mannix[3] also interpreted their catheterization data as representative of a patent ductus with pulmonary hypertension and a right-to-left shunt, their patient having been subjected to thoracotomy for possible ductus repair. In our case, absence of the aortic arch was not suspected from the catheterization data. As already mentioned, the findings were interpreted as a combination of ventricular defect with patent ductus, with a right-to-left shunt into a normal aorta. The demonstration during catheterization of what appeared to be a damped aortic tracing, in reality reflecting an interruption of the aorta, reveals the inadequacies and difficulties attendant upon simple right heart catheterization.

Indications for Selective Angiocardiography: Although absence of the arch is undoubtedly one of the rarest of aortic anomalies, experiences with this defect thus far published indicate that it is a condition amenable to surgery.[4] In consideration of the great advances recently made in the field of repairing complicated congenital cardiac defects, it would seem germane to use every available diagnostic method in such cases, not only to confirm or outline suspected or known deformities, but also to detect completely unsuspected anomalies. The advent of angiocardiography has contributed immeasurably to the understanding of most congenital cardiac defects. However, it is now being argued by some that such dye-contrast studies have served their greatest usefulness and that the risk of the procedure itself does not justify its routine use. We do not believe that such an argument is valid, either from the standpoint of the mortality associated with dye-contrast injection or in consideration of the valuable information gained from such a study. Had angiocardiography been carried out from the right ventricle in the patient described here, it is reasonable to expect that a complete diagnosis could have been made.

This, therefore, raises the question of whether or not a routine selective angiocardiogram should be performed at the conclusion of the regular catheterization in all cases of congenital cardiac disease in infants and young children. We believe that this procedure, performed with the patient under general endotracheal anesthesia with Fluothane, carries an extremely low mortality risk. Recent figures from the literature using similar methods of examination support this hypothesis. Bagger et al.,[5] reporting 2,451 angiocardiographies, mention nine deaths attributable to the procedure itself,

a mortality of 0.4 per cent. Our personal experience, comprising well over 200 such examinations, includes no deaths associated with dye-contrast injection.

Summary

An infant with congenital absence of the aortic arch, patent ductus arteriosus and interventricular septal defect is described. The difficulties encountered in diagnosis even with the utilization of cardiac catheterization are pointed out. In view of possible surgical repair in this and other congenital cardiac defects, the desirability of angiocardiographic studies is emphasized.

Acknowledgment

We are indebted to Drs. Leonard Gettes and James Utterback for the anatomic studies in this report.

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Progress Notes in Cardiology

Edited by EMANUEL GOLDBERGER, M.D., F.A.C.C.

New York, New York

Angiocardiographic Diagnosis of an Anomalous Left Coronary Artery Originating from the Pulmonary Artery

IN INFANCY, the clinical diagnosis of an anomalous origin of the left coronary artery from the pulmonary artery may be suggested by a history of angina-like episodes, the presence of extreme cardiomegaly in the absence of significant murmurs, and an electrocardiographic pattern resembling anterolateral myocardial infarction. However, other conditions, notably endocardial fibroelastosis and myocarditis, may present similar clinical and electrocardiographic pictures. Since the aberrant left coronary artery is the one condition for which surgical correction may prove of benefit, Drs. Norman S. Talner, Aaron M. Stern and Melvin M. Figley (Departments of Pediatrics and Radiology, The University of Michigan Medical Center, Ann Arbor, Michigan) have recently used angiocardiography to establish the definitive diagnosis.

Two female infants, both four months of age, have been studied. The first infant had a typical clinical history, cardiomegaly and an electrocardiographic tracing that suggested posterolateral infarction. A selective angiocardiogram with injection into the main pulmonary artery revealed the anomalous origin of the left coronary artery from the pulmonary artery with flow of dye from the pulmonary artery into the left coronary artery. The second patient had only a history of dyspnea at rest, massive cardiomegaly and an electrocardiographic pattern of left ventricular hypertrophy and T wave changes and was thought to have endocardial fibroelastosis. A venous angiocardiogram again demonstrated the anomalous origin of the left coronary artery from the pulmonary artery. Postmortem studies were obtained on both infants approximately one month after the dye studies and confirmed the angiocardiographic diagnosis.

Reoperation for Pulmonary Stenosis with Cyanosis

THE systemic-pulmonary artery anastomosis for pulmonary stenosis and cyanosis (tetralogy of Fallot) sometimes becomes thrombosed. J. Alex Haller (*Surgery*, 44: 919, 1959) reviewed the records of 1,500 patients with pulmonary stenosis and cyanosis who were operated upon between 1944 and 1957 at The Johns Hopkins Hospital. One hundred and nine required reoperation because the original systemic-pulmonary artery shunt became inadequate. The highest incidence of shunt failure occurred in the infant age group (zero to two years). One in every seven patients required reoperation. The most common cause of a poor result in this group was thrombosis of the anastomosis. The best prognosis was in the five to twelve year age group in which only one patient in twenty-five required a second operation. The indication for a second anastomosis in 70 per cent of these patients was that they had outgrown their original shunts which were still patent and functioning well. In 52 per cent of the second operations a Potts-type anastomosis was employed, but analysis of the postoperative data indicates that the type of shunt has not influenced the generally good result from the second operation. Ten patients died during or shortly after operation, a 9 per cent over-all operative mortality. Eighty-three patients have

been followed more than three months (average follow-up three years) since their second operation; seventy-five (90 per cent) of these are considered to have good postoperative results.

Readings in Cardiology

From time to time, interesting books which ordinarily might escape the attention of cardiologists will be briefly reviewed in these columns.

Anesthesia for the Patient with Chronic Congestive Heart Failure. Recent advances in cardiac surgery have forced both the surgeon and the cardiologist to re-evaluate pre- and postoperative care, particularly in patients with heart disease. The newer aspects of the many problems involved in both normal and cardiac patients are admirably described in a recent book by Dr. Francis D. Moore.* The following is a summary of the description of anesthesia for the patient with chronic congestive heart failure:

"The proper use of anesthesia for patients undergoing cardiac surgery in the presence of severe heart disease forms a whole chapter in itself and, as a specific subject in anesthesia practice and pharmacology, is not our primary concern in this book. The surgeon must be aware of certain basic phenomena in this area so that he may appreciate some of the factors considered by the anesthetist in the choice and administration of anesthetic agents.

"*1. Tachycardia.* In the patient with late valvular heart disease, increasing tachycardia means decreasing cardiac output. In the normal individual the 'danger area' of pulse rate, where increasing pulse rate ceases to produce increasing cardiac output and further tachycardia results in progressively lowered cardiac output, occurs somewhere around a rate of 120 to 140 beats per minute. In the patient with mitral stenosis, this dividing line may occur at much lower pulse rates, even as low as 100. This is responsible for the decreasing cardiac output observed upon exercise in mitral stenosis and is accounted for by the fact that in this disease the diastolic filling is very slow and the patient must have a prolonged diastole in order to develop an adequate ventricular stroke volume. Premedication and induction of these patients should therefore involve a minimum of 'excitement phase' and the use of agents that will not produce tachycardia.

"*2. Oxygenation.* The patient with chronic heart disease has been in a state of borderline oxygenation for many months or years. Any further desaturation will be poorly borne. During his surgical operation it may be possible to provide high oxygen concentrations in the alveolar air and materially improve the patient's ventilation over anything that he has been able to achieve before. Such a step is important. Immediately on extubation the critical time occurs for both anoxia and respiratory acidosis.

"*3. Depth and Duration of Anesthesia.* Patients having surgery for heart disease seem to do better if they can be carried 'light' and if their total anesthesia experience is as short as possible, yet haste is just as dangerous here as in other areas of surgery. While unnecessary prolongation of the surgical operation is not warranted, these patients do well on accurate surgery with good hemostasis and careful asepsis. When the surgeon cuts corners in dealing with the cardiac patient, the thing that suffers first is hemostasis. Elevated venous pressure makes hemostasis difficult in these patients. The accumulation of large postoperative hemothoraces is not unusual in cardiac patients. Elevated venous pressure is one cause of postoperative bleeding, but the sense of urgent hurry is another. If the patient's anesthesia is being well managed, the additional ten to twenty minutes required to secure hemostasis is not going to do the patient's heart any harm. The ravages of postoperative hemorrhage jeopardize his survival much more severely. Rapid but effective operation with good hemostasis and resumption of consciousness within a matter of minutes after the incision is closed, rapid return of normal cough reflex, and minimal use of depressing opiates postoperatively are important.

"*4. Local Anesthesia?* There is a widespread misapprehension that local anesthesia—probably because of its lack of systemic toxicity—is particularly appropriate for these very ill

* Moore, F. D. Metabolic Care of the Surgical Patient. Philadelphia, 1959. W. B. Saunders Co.

patients. The feeling is that such an anesthetic will be less of a 'burden' to the patient.

"The fact of the matter is that the acutely ill cardiac patient, usually an elderly person, apprehensive and dyspneic, is placed in a very uncomfortable position for surgery. The patient's breathing may be orthopneic. A supine position on the operating table is in itself uncomfortable and even hazardous. The patient is nervous, and any increased tachycardia, pain or apprehension further compromises both forward flow and retrograde failure. Local anesthesia presents a hazard in all these departments. Except for the most minor types of surgery, local anesthesia is highly undesirable for the ill patient with heart disease. This is true of most of the 'bad anesthesia risks,' whose care is further complicated by the use of an inadequate anesthetic. Far preferable is the high oxygen concentration available through an endotracheal tube and the rest, quiet, relaxation and insensibility to pain that are produced by a light plane of anesthesia such as is obtainable with cyclopropane, thiopental, or nitrous oxide with curare."



Workmen's Compensation for the Cardiac

Edited by LOUIS H. SIGLER, M.D., F.A.C.C.

Brooklyn, New York

Acute Myocardial Infarction Following an Emotional Disturbance

IN a previous report[1] I discussed the subject of emotional disturbance as a cause of an acute cardiac insult. I presented some of the possible physiologic and pathologic changes responsible for such an insult under emotional strain.

The following case, which was sent to me for review by a physician from Los Angeles, further illustrates the causal relationship between a severe emotional upset and an acute myocardial infarction. The case is of interest because the condition occurred in an apparently perfectly healthy person, forty-two years of age, an airplane pilot who usually is not easily disturbed by danger or by an exciting event. It also illustrates the intermittency of subjective manifestations as the pathologic process progressed for about two days before the diagnosis was established. During this interval there were periods when he felt quite well, and even piloted his plane over a stretch from the West Coast to Hawaii without discomfort.

It is hoped that more cases illustrating the effect of emotion and strain upon the heart will be brought to our attention.

CASE REPORT*

A forty-two year old married man, an air pilot by profession for fourteen years, witnessed an airplane explosion in the air in the middle of the night while on duty at the airport. Two of his friends who were pilot and co-pilot on this plane were killed. He suffered a severe emotional disturbance and one minute later he experienced severe pain in the center of his chest which lasted for a few minutes. The next morning, at or about 9:30 A.M., while on the flight line getting ready for his flight, the pain recurred and again lasted only a couple of minutes. He got into his plane and flew it to Honolulu. During the flight, he felt fine. After reaching Honolulu he had several hours of sleep; when he got up he again experienced discomfort in his chest. He consulted a doctor in Honolulu, who told him that he had "angina pectoris." A short time after he left the doctor's office he had another attack, which was more severe and intense. He returned to the doctor's office where he was given an injection and transferred to a hospital; he was told that he had had a "heart attack" and was given oxygen. He was treated in the hospital for six weeks. Since his discharge from the hospital he has felt quite well, but has not returned to work.

The family history was non-contributory. His past personal history revealed nothing abnormal. He had always enjoyed excellent health. During World War II he flew with the Flying Tigers Squadron. At no time before did he have any indigestion, shortness of breath or discomfort in his chest. There was no history of high blood pressure or nervous disorder.

Examination about three months after the attack when I first saw him revealed a white man of small stature who was well nourished and looked his stated age; he appeared intelligent, cooperative and was in no apparent pain or discomfort. He weighed 149 pounds, and was 65 inches tall. The chest and lungs were normal. The heart showed no increase in dullness, and the sounds were regular in rhythm, of fair tone and quality. No murmurs were heard. The blood pressure was 110/90 mm. Hg.

* Submitted by ROMEO J. LAJOIE, M.D., Los Angeles, California.

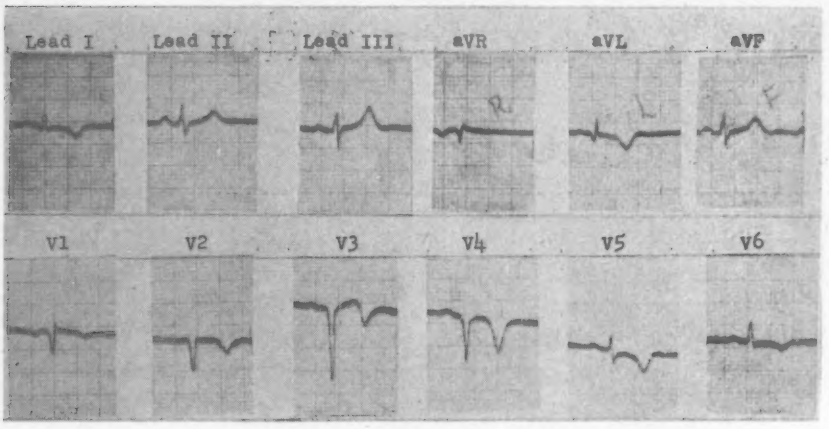


FIG. 1. Healed infarction of the anterior wall.

An electrocardiogram (Fig. 1) revealed evidence of healed infarction of the anterior wall of the left ventricle.

Comment: The diagnosis was coronary atherosclerosis with recent coronary occlusion and infarction of the anterior wall which was healed. It was believed that there was direct causal relationship between the emotional disturbance of witnessing the airplane explosion and the acute coronary attack. We cannot deny pre-existing coronary atherosclerosis.

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Book Reviews

Textbook of Pediatrics, edited by Waldo E. Nelson. W. B. Saunders Company, Philadelphia, 1959, pp. 1,462, $16.50.

This textbook continues to be the "Bible" for both the student and practitioner of pediatrics. It fully accomplishes its purpose in approximating a complete coverage of the field of pediatrics but in so doing a fair amount of necessary detail in the various subjects is lost. In some instances this is unfortunate but by and large no great void is evident. Although there are eighty-one contributing authors, each section seems to flow in the same simple, clear, concise style so that different authorship is never obvious. Its simplicity affords easy and rapid access to a gross description of most of the conditions encountered in the field of pediatrics.

The section on the cardiovascular system was contributed by Drs. Samuel Kaplan and Robert A. Lyon and consists of eighty-four reasonably well illustrated pages. The portions of this section devoted to electrocardiography and cardiac catheterization will afford the student an adequate working knowledge of these diagnostic tools to which further detail can be added by consulting some of the more complete textbooks of pediatric cardiology. Those portions devoted to the specific congenital lesions seem only able to afford the student with an awareness of the various types of lesions but hardly enough detail with which to make a clinical diagnosis. This is a bit unfortunate and yet, in keeping with the tone of the remainder of the text, more detail could hardly be expected. This portion, however, is very well organized and should give to the student a clear picture of a certain orderliness about the congenital lesions. Greater detail is provided for some of the more common conditions such as patent ductus arteriosus and coarctation of the aorta. Unfortunately, not quite enough is devoted to the atrial and ventricular septal defects, both of which are quite commonly encountered in pediatrics and generally afford somewhat greater difficulties in diagnosis.

The section on rheumatic fever, consisting of ten pages, is contributed by Dr. Ann G. Kuttner and is quite a complete review of this subject. Dogmatism, particularly so far as therapy is concerned, is fortunately avoided.

No attempt has been made to provide a comprehensive bibliography but it is designed to include references to articles which themselves contain extensive bibliographies in as many subjects as possible.

This book is a "must" for every pediatrician's bookshelf but is not necessarily recommended for the cardiologist since his needs are much more extensive than can be provided for in this text.

RAPHAEL N. PAUL, M.D.

Coronary Heart Disease, by John W. Gofman. Charles C Thomas, Springfield, Ill., 1959, pp. 353, $8.00.

In 1950 the National Advisory Heart Council initiated a project designed to compare the relative accuracy of serum lipoproteins (determined by the ultracentrifuge technic of Gofman) vs. serum cholesterol levels in predicting the occurrence of new cardiovascular events in previously normal subjects.

It is suggested that any prospective reader of Dr. Gofman's book who has not yet come to a conclusion in the cholesterol-lipoprotein controversy first read the report on this project (*Circulation*, 14: 691, 1956). If he then believes that the ultracentrifugal lipoprotein determination is the best method currently available for predicting the occurrence of atherosclerosis, Dr. Gofman's volume will be of great interest to him. However, if his conclusion is that the simpler and less expensive serum cholesterol determination is at least as accurate a prognosticator as the lipoprotein analysis, he will find little of value in "Coronary Heart Disease," inasmuch as this book is based on the premise that the lipoprotein determination is the most valuable laboratory guide for the practicing physician interested in atherosclerosis.

A clinicopathologic discussion of coronary disease and the development of the Gofman technic for studying the lipids presumably involved in atheromatosis are presented in the opening chapters. The ultracentrifuge method separates various groups of lipoproteins according to their speed of inward migration (flota-

tion). Lipoproteins involved in atherogenesis in human beings are of very low density and occur in the range of S_f0 to S_f400. To integrate different lipoprotein classes in a single figure, Dr. Gofman formulated the atherogenic index,

$$AI = \frac{S_f0\text{–}12 + 1.75\ S_f12\text{–}400}{10} \text{ in mg. per cent.}$$

Male patients with previous myocardial infarctions had been found to have significantly higher atherogenic indices than age-matched normal subjects. Dr. Gofman later showed that the lipoproteins were also higher in normal men who subsequently developed infarcts than in the base population from which they were drawn. A predictive value for the lipoproteins was thus established.

The author then proceeds to compute the risk of development of coronary disease using both the atherogenic index and the diastolic blood pressure; to show the familial predisposition to atherosclerosis by a retrospective study of family histories of males with and without coronary disease; to develop the concept of the atherogenic index and the diastolic blood pressure as accumulative factors, thereby explaining the increased incidence of coronary disease with increasing age; and to indicate that the more frequent occurrence of coronary disease in obese persons is accounted for almost completely by the diastolic blood pressure and atherogenic index rather than by the overweight *per se*.

The question of the influence of diet on the lipoproteins is then raised and the use of a low fat diet for lowering any elevated atherogenic index is indicted by Dr. Gofman, who believes that dietary fat increases certain lipoprotein fractions, but that dietary carbohydrate increases others.

Cigarette smoking (which raises the atherogenic index); diabetes (the increased predisposition of the patient with diabetes to coronary artery disease is not due to the diabetes *per se*); thyroid gland (thyroid substance lowers the atherogenic index even in subjects with normal thyroid function); and occupation-stress-physical activity (physically active occupations lower the atherogenic index; "stress" exerts its effect through dietary means) are then discussed at some length.

Following a very brief presentation of the lipoprotein vs. cholesterol controversy, the author concludes with a résumé of therapeutic regimens designed to reduce elevated atherogenic index values.

The book reads easily, but is not written with the conciseness of style that has characterized Dr. Gofman's earlier scientific papers. The discussion of the ultracentrifuge technic and the genesis of the atherogenic index are of interest. As stated originally, the volume is recommended for those who believe that this technic is productive of sufficient information of unique clinical importance to warrant its great expense.

To those who are not yet convinced of the superiority of this determination over any other currently in use, data taken directly from the study by the National Advisory Heart Council may be of interest. In assessing the relative values of the atherogenic index vs. serum cholesterol in their respective abilities to predict the occurrence of myocardial infarction, the ability to segregate the potential risks into a small part of the sample is of importance. The following table gives the percentage of new coronary events developing over a two-year period in presumably normal men whose original atherogenic indices or serum cholesterol levels were above the median value of the base population (upper 50 per cent).

Determination	New Events	No. in Upper 50 Per Cent	Per Cent
Gofman's Material (1,704 Men in Base Population)			
Atherogenic index	19	16	84
Cholesterol	17	14	82
Total Material, Including Gofman's (3,985 Men in Base Population)			
Atherogenic index	37	33	89
Cholesterol	37	32	86

A majority of the study team could not support Dr. Gofman's contentions. For those who agree with that majority, "Coronary Heart Disease" will provide little more than a one-sided reference work on a subject which is still controversial. LOUIS E. SCHAEFER, M.D.

Peripheral Vascular Diseases: An Objective Approach, by Travis Winsor. Charles C Thomas, Springfield, Ill., 1959, pp. 845, $16.50.

This book attempts to present a simple approach to the study of peripheral vascular disorders. To achieve such an aim, reliance is placed, in great part, on the use of a large

number of page- and half-page–sized illustrations, all based on bold line drawings. Some of these are excellent. However, many are quite elementary and, in the opinion of the reviewer, do not contribute enough to the elucidation of the text to warrant the relatively large amount of space allocated to them.

The first three chapters are devoted to the physiology and anatomy of the peripheral circulation. The diagrammatic representation of the various arterial and venous collateral circulations which take over following obstruction of the main channels is instructive and constitutes a simple means of describing these vascular changes. The dynamics of the circulation are also presented in a simple and adequate manner. The microcirculation, which has been the subject of much investigation in recent years, is only touched upon.

About one-fourth of the book (nineteen chapters) deals with tests for determining the state of the circulation. More than half of this section is devoted to a detailed description of procedures of a laboratory nature, such as ergography, radioisotopes, scleral vascular and capillary nail microscopy, calorimetry, plethysmography of various types and physiologic transducers. The subject of digital plethysmography, a field in which the author is an authority, is discussed at much length. In the Preface it is pointed out that the purpose of this monograph is to present through such improved instruments "an objective approach to the understanding and treatment of patients with peripheral vascular disease."

Methods which require hospital facilities, such as infrared photography, measurement of venous pressure, sweating patterns, venography, arteriography and vasodilating procedures, are also presented in detail. The remainder of the section is devoted to a discussion of tests that can be utilized at the bedside or in the office, such as oscillometry, ophthalmoscopy and skin thermometry.

Two chapters deal with taking of the history and with the method of performing a routine examination, as well as one of the peripheral circulation. The basis for abnormal alterations in temperature and color of the skin, for the various types of pain associated with different categories of vascular disorders, and for trophic changes is presented.

The last twenty-three chapters of the book are devoted to a presentation of clinical entities. Such relatively common disorders as arteriosclerosis obliterans, thromboangiitis obliterans, arterial and arteriovenous aneurysms, and Raynaud's disease, as well as such rare entities as ainhum, acrocyanosis, livedo reticularis and tumors of blood and lymph vessels are presented. The subject of the diseases of veins is discussed in one chapter, with the result that the postphlebitic syndrome, phlebothrombosis, varicosities and deep thrombophlebitis are only touched upon lightly. A chapter is devoted to diseases of the capillaries.

The last two chapters in this section deal with the treatment of peripheral vascular disorders, although specific therapeutic measures are also included in the sections devoted to a discussion of clinical entities. Emphasis is placed on the various new surgical approaches to the problem.

This book may be useful to the medical student, the house staff and the general practitioner in serving as an introduction to peripheral vascular disorders. However, to such groups, the large segment of text dealing with laboratory procedures may prove of little value. D. I. A.

College News

President's Column

I CONSIDER it a great honor and a privilege to be able to serve the American College of Cardiology for the coming year. I am well aware of the record of my predecessors and how much each has done to bring the American College of Cardiology to its present stature.

During the coming year I shall make every effort to carry on the many projects that have been previously initiated, and I have already received many thoughts and ideas for the future of our College. I will welcome from all of our Fellows, Associates and Members their ideas and critical evaluation of what we are trying to do. A college, in my opinion, cannot be successful unless everyone connected with it takes an active interest in its present and in its future.

All of you who attended the Annual Meeting in Indianapolis are well aware of the fine program and of the success of the meeting. In particular this gives me a chance to again publicly thank our Indianapolis members and friends of the College for all they did for us. One of the most inspiring parts of the meeting to me was the program presented at the First Scientific Session under the chairmanship of Dr. John B. Hickam of the work of the young research workers in cardiology from the University of Indiana.

There were too many other highlights of the convention to enumerate them, but I think all of us who were there will remember the address of Dr. Samuel A. Levine on "Some Prevalent Errors in the Practice of Cardiology." This in a sense gave us a short review of much of the lifework of one of America's great cardiologists.

The importance of the humanities in medicine was recognized by the founder of our College and was restated so well by Dr. John Barlow Youmans. All of you who did not hear the Groedel Lecture will certainly want to read it in the Journal.

One of the things that is good for a college is that meetings are not always held in the largest cities, but in a smaller city like Indianapolis. This has, in my opinion, many advantages that are not always recognized. There are not so many outside diversions, so that the meeting becomes much more closely knit and gives those who attend the opportunity to know each other better in a friendly way. After all, one of the purposes of the American College of Cardiology is the opportunity for friendly fellowship that must exist among us.

On assuming the office of the President, there are many things that have to be done, and I hope to keep you informed of what is taking place in our College. Some of the immediate things are the appointment of committees, the selection of new Governors and, of course, of particular importance, organization for the New York City meeting next year must be immediately started. As all of you know, our Interim Meeting with the American Heart Association will be in St. Louis, October 21 to 23, 1960.

LOUIS F. BISHOP

Election of Officers

NEWLY elected officers of the American College of Cardiology are as follows: President-Elect, E. Grey Dimond; First Vice-President, Robert Leslie; Second Vice-President, John W. Patterson; Third Vice-President, C. Walton Lillehei; Secretary, John S. LaDue; Assistant-Secretary, Irving Brotman; Treasurer, William L. Wheeler, Jr.; Assistant-Treasurer, Henry I. Russek; Trustees for five years, Dwight E. Harken, Eliot Corday, Edgar Hull and Robert P. Grant.

Pensacola Workshop: The College in Action

JUNE 9 TO 11, 1960

AN OUTSTANDING experience was afforded the colleagues of our College who attended the workshop on "Effect of Stress on the Cardiovascular System; Space Medicine." Capt. Ashton Graybiel, MC USN, was ably assisted by Comdr. Neal D. Sanborn, MC USN; Lt. Comdr. Seldon Creighton Dunn, MC USN; Lt. Sr. Gr. Arthur J. Moss, MC USN; Lt. Sr. Gr. Robert K. Osborne, MC USN; and Lt. Sr. Gr. John A. Lowder, MC USN, of the Naval Aviation Medical Center, Pensacola, Florida.

Transitory Hypertension and Air Force Training: Two long-term studies of a group of young people with mild benign hypertension were reviewed. Based upon their findings, the investigators concluded that even an occasional elevation of blood pressure (140/90) warrants rejection for training as pilot in the Air Force. Training of an aviator costs the Government well over $20,000 and, in their opinion, a potential hypertensive is at least a financial risk.

Ballistocardiography in Relation to Aging: Ballistocardiography was evaluated in relation to the aging process of the cardiovascular system. It was emphasized that cardiovascular aging is a complex phenomenon associated with gradual yet progressive deterioration of cardiovascular function.

The rate of aging and the extent of coronary and myocardial involvement vary widely in different people. Coronary atherosclerosis is not limited to older age groups. Evidence of it is seen in a large number of young, apparently healthy males between twenty and forty years of age.

The investigators at the School of Aviation Medicine, therefore, are constantly looking for better and more accurate methods of determining the degree of aging of the cardiovascular system. They now employ an ultra-low frequency acceleration ballistocardiograph of their own design as part of such a study. Their present conclusions, which will soon be published, are as follows: "The mean HI angle remains rather constant without significant change with age. The mean HI and HJ amplitudes as well as the mean HK/HI ratio show progressive almost linear age-related changes." This may prove significant in the study of rapidity of cardiovascular aging.

Effort and the Work Electrocardiogram of the Superfit: Convincing evidence was presented that in the superfit person a greater amount of work is necessary to bring about electrocardiographic changes suggestive of coronary insufficiency.

Space Medicine: After a comprehensive introductory chat, movies of the effect of zero G on man and of the famous Russian space-traveling dogs were shown. The training necessary to condition such animals was excellently demonstrated. The men were then introduced to monkey Baker of space fame and were given a detailed description of the preparations for launching and retrieving.

The participants had an opportunity to be rotated in the so-called "Human Centrifuge." This is quite an experience.

It was gratifying to be told by members of the staff of the School of Aviation Medicine that the College participants "made a wonderful sounding board" to help their evaluation of the work done. This statement confirmed that the College Workshops are an excellent medium for men of scientific calling who wish to keep abreast of progress. A few days of "on-the-spot" interchanges of experiences among colleagues is unequaled in its benefits.

Chairman, JOSEPH B. WOLFFE, M.D.
Clinical Workshop Committee
American College of Cardiology

Announcements

College to Hold Tenth Interim Meeting

The tenth interim meeting of the American College of Cardiology will be held in conjunction with the annual sessions of the American Heart Association in St. Louis, Missouri from October 21 to 23. The scientific program will include a joint session on clinical cardiology on Friday morning, October 21, 1960 and the Fireside Conferences will be held Friday evening, October 21, 1960.

New Society Founded

The Society for Ballistocardiographic Research was founded on April 14, 1960 during its First Congress under the presidency of Professor H. C. Burger, Utrecht, Holland. Applications for membership should be directed to the Secretary, Abraham Noordergraaf, PH.D., Dept of Medical Physics, Physics Laboratory, Bylhouwerstraat 6, Utrecht, who will also accept orders for the *Proceedings* of the First Congress. The society is a sister-organization of the Ballistocardiograph Research Society, founded by Dr. Isaac Starr several years ago.

Persons living in North and South America may apply for membership and obtain information by writing to the Secretary of the Ballistocardiograph Research Society, DeWitt H. Smith, M.D., New Jersey Psychiatric Institute, P. O. Box 1000, Princeton, New Jersey.

Membership of both Societies is limited to those who are actively engaged in ballistocardiographic research.

Postdoctoral Training Offered by Chicago Medical School

Postdoctoral training in either Clinical or Experimental Cardiology is offered by the Division of Cardiology of The Chicago Medical School at Mount Sinai Hospital, Chicago. The program of training is supported by the National Heart Institute, U. S. Public Health Service.

Physicians having some training in Clinical Cardiology or a PH.D. in Experimental Physiology will receive preference.

Information concerning the program of training and stipend may be obtained by writing to Dr. A. A. LUISADA, Program Director, 2755 West 15th Street, Chicago 8, Illinois.



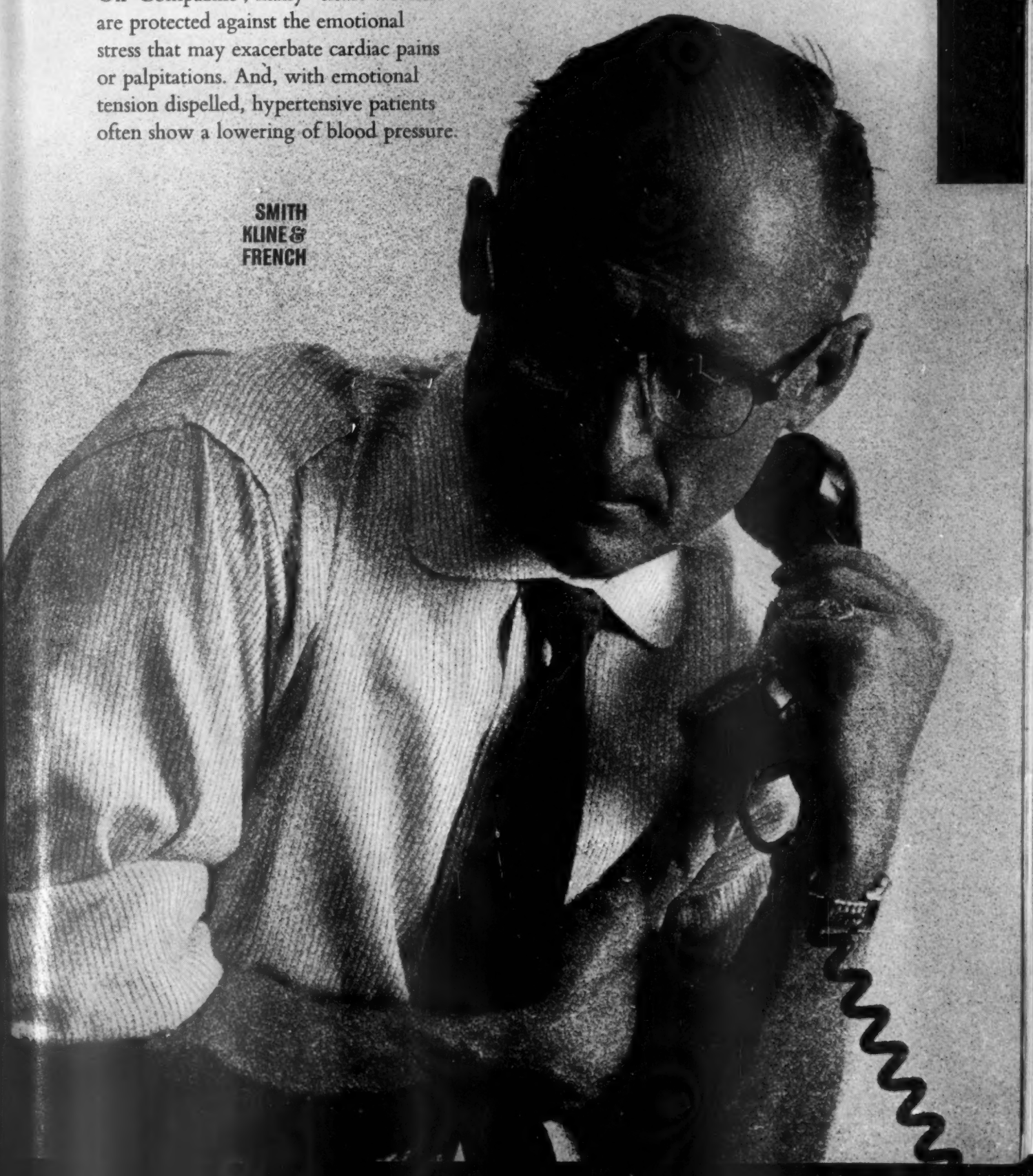


in cardiac patients · Compazine®

brand of prochlorperazine

reduces the impact of emotional stress—
relieves fear and apprehension.
On 'Compazine', many "heart worriers"
are protected against the emotional
stress that may exacerbate cardiac pains
or palpitations. And, with emotional
tension dispelled, hypertensive patients
often show a lowering of blood pressure.

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THE FACTS ABOUT MER/29

MER/29 *reduces total body cholesterol in 8 out of 10 —and these are the patients most likely to benefit*

your patient with high cholesterol levels...

MER/29 reduces both serum and tissue cholesterol, irrespective of diet.[1] In 463 patients, the mean cholesterol was reduced from 324 mg.% to 253 mg.% — an average decrease of 71 mg.%.[1-8]

your patient with angina pectoris...

concurrent benefits have been reported in some patients receiving MER/29. These include decreased incidence and severity of attacks, improved ECG patterns, diminished nitroglycerin requirements, and increased sense of well-being.[1,4,6-8]

your patient with postmyocardial infarction...

while more time is needed to determine the over-all prognostic significance, it has been observed that MER/29 "... reduced morbidity and mortality rates below those of control series during the first year following coronary thrombosis."[4]

your patient with generalized atherosclerosis...

atherosclerosis "... has been shown to afflict about 77% of American males as early as in the 20-to-30 age range."[9] With MER/29 you have a new, well-tolerated means of lowering cholesterol — which has been considered "... the *sine qua non* of the atheromatous lesion."[9]

compatible with other cardiovascular therapies: MER/29 can be used along with other measures to control anxiety, hypertension, obesity, and other conditions associated with cardiovascular disorders. These include anticoagulants, nitroglycerin, and PETN.

safety data: Patients have now been treated with MER/29 for relatively long and continuous periods. In no case has there been evidence of serious toxic effects on the function of any vital organ or system. However, since long-term MER/29 therapy may be necessary, periodic examinations, including liver-function tests, are desirable. Side effects (nausea, headache, dermatitis) are rare and have usually been associated with dosages greater than those recommended for effective therapy.

contraindication: Pregnancy. Since MER/29 inhibits cholesterol biosynthesis, and cholesterol plays an important role in the development of the fetus, the drug should not be administered during pregnancy.

supplied: Bottles of 30 pearl gray capsules.

. . . the first cholesterol-lowering agent to inhibit the formation of excess cholesterol within the body, reducing both tissue and serum cholesterol

. . . no demonstrable interference with other vital biochemical processes reported to date

. . . convenient dosage: one 250 mg. capsule daily before breakfast

. . . toleration and absence of toxicity established by 2 years of clinical investigation

MER/29

(triparanol)

References: 1. Hollander, W., and Chobanian, A. V.: Boston M. Quart. *10*:37 (June) 1959. 2. Oaks, W., and Lisan, P.: Fed. Proc. *18*:428 (Mar.) 1959. 3. Oaks, W. W., *et al.*: A. M. A. Arch. Int. Med. *104*:527 (Oct.) 1959. 4. Lisan, P.: Proceedings, Conference on MER/29, Progr. Cardiovasc. Dis. *2*:(Suppl.)618 (May) 1960. 5. Oaks, W. W.: *Ibid.*, p. 612. 6. Hollander, W., *et al.*: *Ibid.*, p. 637. 7. Halperin, M. H.: *Ibid.*, p. 631. 8. Toro, J.: *Ibid.*, p. 544. 9. Morrison, L. M.: J.A.M.A. *173*:884 (June 25) 1960.

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TRADEMARK: "MER/29"

"First in the hearts" of cardiac patients

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CARDIAC CATHETERS

A.C.M.I. was the first to introduce nylon woven catheters in the United States – originally for ureteral use – later for cardiac catheterization.

A.C.M.I.'s nylon woven cardiac catheters are preferred for smoothness combined with flexibility. Lengths: 30 cm. to 150 cm. Thin-walled, radiopaque.

A.C.M.I.'s polyethylene cardiac catheters provide a smoother and larger lumen for collection of blood samples and the rapid injection of contrast media. Other types too are under development.

A triumph of technical skill – all A.C.M.I. cardiac catheters have earned the confidence of the medical profession through their consistently superior quality.

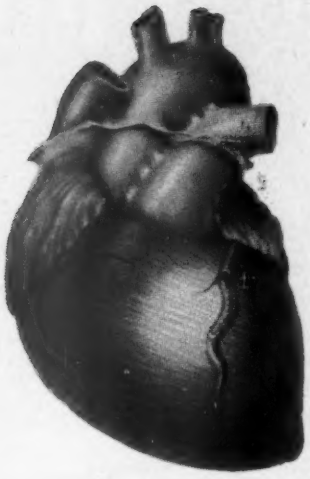
Nylon woven cardiac catheters

A·C·M·I· TRADE MARK

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American Cystoscope Makers, Inc.

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IN ANGINA PECTORIS AND CORONARY INSUFFICIENCY

... the treatment must go further than vasodilation alone. It should also control the patient's ever-present anxiety about his condition, since anxiety itself may bring on further attacks.



AFTER MYOCARDIAL INFARCTION

... it is frequently not enough to boost blood flow through arterial offshoots and establish new circulation. The disabling fear and anxiety that invariably accompany the condition must be reduced, or the patient may become a chronic invalid.

Protects your coronary patient better than vasodilation alone

Unless the coronary patient's ever-present anxiety about his condition can be controlled, it can easily induce an anginal attack or, in cases of myocardial infarction, considerably delay recovery.

This is why Miltrate gives better protection for the heart than vasodilation alone in coronary insufficiency, angina pectoris and postmyocardial infarction. Miltrate contains not only PETN (pentaerythritol tetranitrate), acknowledged as basic therapy for long-acting vasodilation. What is more important — Miltrate provides Miltown, a tranquilizer of *proven* effectiveness in relieving anxieties, fear and day-to-day tension in over 600 clinical studies.

Thus, your patient's cardiac reserve is protected against his fear and concern about his condition...and his operative arteries are dilated to enhance myocardial blood supply.

Supplied: Bottles of 50 tablets. Each tablet contains 200 mg. Miltown and 10 mg. pentaerythritol tetranitrate.
Dosage: 1 or 2 tablets q.i.d. *before meals* and at bedtime, according to individual requirements.

REFERENCES

1. Ellis, L. B. *et al.:* Circulation *17*:945, May 1958. **2.** Friedlander, H. S.: Am. J. Cardiol. *1*:395, Mar. 1958. **3.** Riseman, J.E.F.: New England J. Med. *261*:1017, Nov. 12, 1959. **4.** Russek, H. I. *et al.:* Circulation *12*:169, Aug. 1955. **5.** Russek, H. I.: Am. J. Cardiol. *3*:547, April 1959. **6.** Tortora, A. R.: Delaware M. J. *30*:298, Oct. 1958. **7.** Waldman, S. and Pelner, L.: Am. Pract. & Digest Treat. *8*:1075, July 1957.

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Over 60 published papers since 1953....



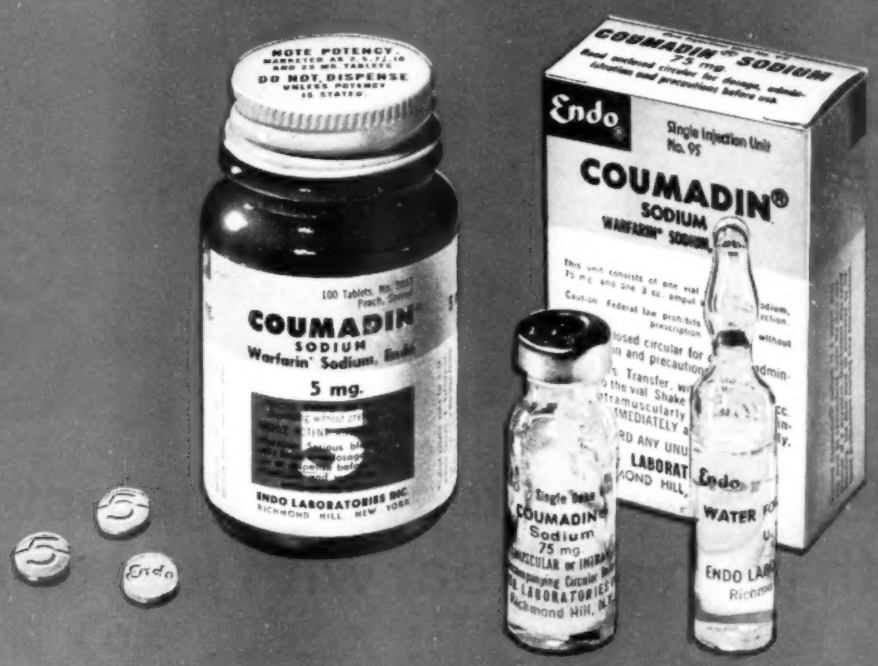
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the proven anticoagulant

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COUMADIN is the *original* and *only* warfarin responsible for establishing this drug as closely approaching the ideal anticoagulant.[1,2]

Over ~~101,000,000~~ 114,000,000 doses administered to date...



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FOR ORAL, INTRAVENOUS OR INTRAMUSCULAR USE

Full range of oral and parenteral dosage forms — COUMADIN* (warfarin sodium) is available as: *Scored tablets*—2 mg., lavender; 5 mg., peach; 7½ mg., yellow; 10 mg., white; 25 mg., red. Single Injection Units—one vial, 50 mg., and one 2-cc. ampul Water for Injection; one vial, 75 mg., and one 3-cc. ampul Water for Injection.

Average Dose: Initial, 40-60 mg. For elderly and/or debilitated patients, 20-30 mg. *Maintenance,* 5-10 mg. daily, as indicated by prothrombin time determinations.

1. Baer, S., et al.: J.A.M.A. 167:704, June 7, 1958. 2. Moser, K. M.: Disease-a-Month, Chicago, Yr. Bk. Pub., Mar., 1960, p. 13.

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Richmond Hill 18, New York



in angina pectoris...

24-hour protection against both pain and fear with just one

COROVAS® Tymcap b.i.d.

Clinically proved[1,2,3] to establish peak nitrate blood levels soon after an initial dose and to maintain these levels throughout a 12-hour period...

thus avoiding bothersome t.i.d. or q.i.d. routines, yet permitting the patient to enjoy up to 12 hours' uninterrupted relief from pain and fear with a single COROVAS Tymcap: "...it would appear that 60 mg. of PETN in TD capsule form [timed-disintegration COROVAS Tymcaps] is as effective as 80 mg. PETN in tablet form, in controlling the anginal attacks."[3]

COROVAS Tymcaps

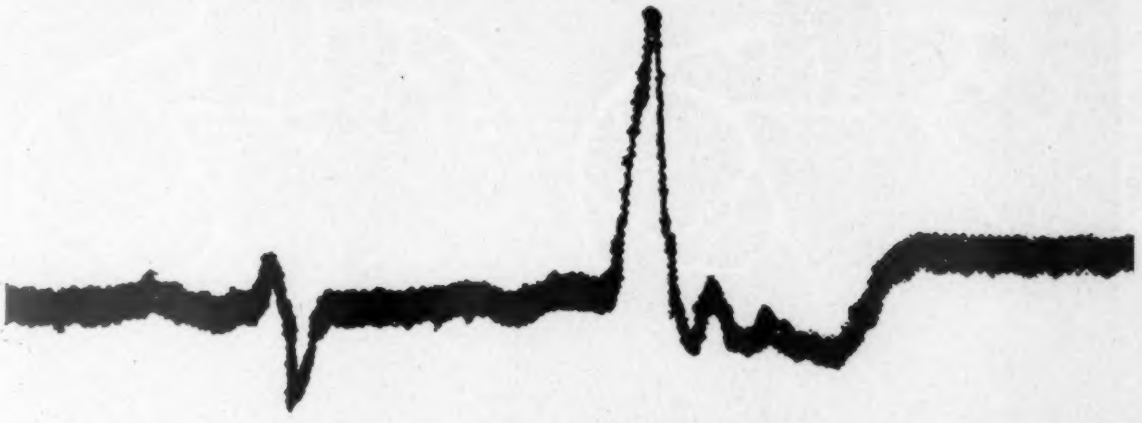
prolonged, sustained-action of vasodilating pentaerythritol tetranitrate (PETN) 30 mg., and sedative secobarbituric acid 50 mg.

- *controls or prevents anginal pain*
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- *reduces the need for nitroglycerin*

Supplied—Boxes of 60 and 120

1. Feinblatt, T. M., and Ferguson, E. A.: New Eng. J. Med. 256:331 (Feb.) 1957.
2. Kupersmith, I. H.: International Record of Medicine, Vol. 171 No. 10 (Oct.) 1958.
3. Berry, J. W., and Roach, T. C.: Circulation, Vol. 17, No. 6 (June) 1958.

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for cardiac arrhythmias... obvious advantages

PRONESTYL® HYDROCHLORIDE

SQUIBB PROCAINE AMIDE HYDROCHLORIDE

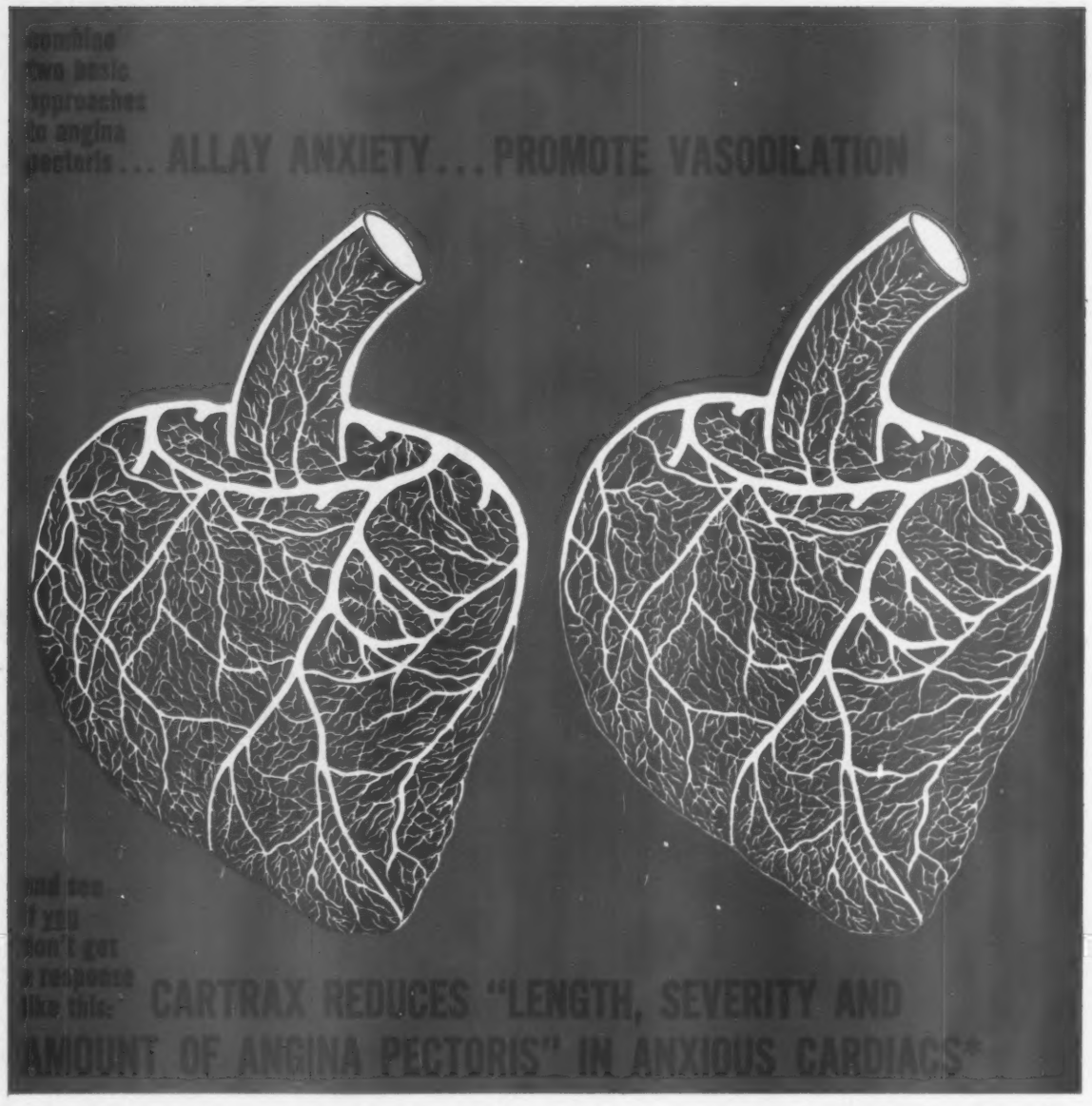
Pronestyl offers obvious advantages over quinidine and procaine in the management of cardiac arrhythmias: "Procaine amide [Pronestyl] should be the drug of choice in arrhythmias of ventricular origin." [1]—on oral administration, side effects are less marked than with quinidine—administered I. V., Pronestyl is safer than a corresponding I.V. dose of quinidine—administered I. M., Pronestyl acts faster than I. M. quinidine[2]—Pronestyl sometimes stops arrhythmias which have not responded to quinidine[3,4]—Pronestyl may be used in patients sensitive to quinidine—more prolonged action, less toxicity, less hypotensive effect than procaine—no CNS stimulation such as procaine may produce.

Supply: For convenient oral administration: Capsules, 0.25 gm., in bottles of 100.
For I. M. and I. V. administration: Parenteral Solution, 100 mg. per cc., in vials of 10 cc.

References: 1. Zapata-Diaz, J., et al.: Am. Heart J. 43:854, 1952. 2. Modell, W.: in Drugs of Choice, C.V. Mosby Co., St. Louis, 1958, p. 454. 3. Kayden, H. J., et al.: Mod. Concepts Cardiovasc. Dis. 20:100. 1951. 4. Miller, H., et al.: J.A.M.A. 146:1004, 1951.

SQUIBB *Squibb Quality—the Priceless Ingredient*

'PRONESTYL'® IS A SQUIBB TRADEMARK



Clark treated 31 anginal patients who showed signs of anxiety, fear, excitement and other forms of emotional stress. On CARTRAX, all 31 fared better than they had on previous therapy... as judged both by subjective reports and by reduced nitroglycerin requirements.*

CARTRAX combines PETN (for prolonged vasodilation) with ATARAX (the tranquilizer preferred for angina patients because of its safety and mild antiarrhythmic properties). Thus, CARTRAX helps you to cope with both components of angina pectoris—circulatory **and** emotional.

For a better way to help your angina patients relax, prescribe CARTRAX.

*Clark, T. E., In press.

CARTRAX®

PETN†+ATARAX®†† **Dosage:** Begin with 1 to 2 yellow CARTRAX "10" tablets (10 mg. PETN plus 10 mg. ATARAX) 3 to 4 times daily. For dosage flexibility, CARTRAX "20" (pink) tablets (20 mg. PETN plus 10 mg. ATARAX) may be utilized at a level of one tablet three to four times a day. The tablets should be administered before meals for optimal response. For convenience, write "CARTRAX 10" or "CARTRAX 20." As with all nitrates, use with caution in glaucoma. **Supplied:** In bottles of 100. Prescription only.

†pentaerythritol tetranitrate ††brand of hydroxyzine

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"excellent control . . . in 54 out of 59 cases [including 43 patients with coronary thrombosis]."[1]

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"It leads to an initial rapid fall in prothrombin activity. . . ."[2] Therapeutic levels attained in 48 to 72 hours.

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"Normal prothrombin levels were recorded between 36 and 72 hours after cessation of treatment. . . ."[3]

prompt reversibility

Vitamin K_1 "... counteracted the effect of Miradon in a predictable fashion in 5 to 8 hours."[4]

prompt restoration

"The anticoagulant effect can be restored rapidly by remedication."[2]

stable maintenance

With MIRADON "...a very even response was evident during therapy."[3] "Once the prothrombin levels had been reduced to the therapeutic bracket, they were maintained there with little difficulty on daily doses of the drug."[5]

References: (1) Blaustein, A.: New York J. Med. *58*:701, 1958. (2) Lange, K., *et al.*: Am. Heart J. *55*:73, 1958. (3) Kellaway, G.: Brit. M. J. *2*:889, 1958. (4) Connell, W. E., and Mayer, G. A.: Canad. M.A.J. *80*:785, 1959. (5) Paul, H. A.: Arscott, P. M.; Koppel, J. L., and Olwin, J. H.: Surg. Gynec. & Obst. *108*:605, 1959.

5-440

"Are the xanthines effective in ANGINA PECTORIS ?"

(Abstract of the paper with above title)

A favorable response was unequivocally demonstrated with aminophylline when administered intravenously to angina pectoris patients. In sharp contrast the author, noted for his original contributions to cardiovascular research, found oral administration ineffective in all patients tested. This suggested that the failure was correlated with subthreshold theophylline blood-levels obtained with oral administration.

A 20% alcohol-solution of theophylline (Elixophyllin®) has been shown to provide blood levels comparable to those obtained with I.V. administration of aminophylline. This oral preparation and a placebo (identical in appearance, taste and alcoholic content) were tested by the electrocardiographic response obtained and by a double-blind clinical evaluation.

The author reported: "In the light of these findings, conclusions derived from animal experiments which have classed theophylline as a 'malignant' coronary vasodilator must be rejected for man." Elixophyllin administered orally to 30 patients was effective "not only in control of symptoms but in its modifying action on the electrocardiographic response to standard exercise. The efficacy of this preparation is based on the rapid absorption and attainment of high blood levels made possible by the vehicle employed."

(Russek, H. I., Am. J. Med. Sc. Feb., 1960)

CLINICAL REFERENCE DATA ON

ELIXOPHYLLIN®

FORMULA:	A hydro-alcoholic solution of theophylline. Each 15 cc. (1 tablespoonful) contains 80 mg. theophylline (equivalent to 100 mg. aminophylline) and 20% ethyl alcohol.
ORAL DOSAGE:	First 2 days—doses of 45 cc. t.i.d. (before breakfast, at 3 P.M., and on retiring). Thereafter—doses of 30 cc. t.i.d. (at same times).
AVAILABLE:	Prescription only; bottles of 16 fl. oz. and 1 gallon.
SPECIAL REPRINT:	Reprint of Dr. Russek's paper abstracted above on request.

Sherman Laboratories

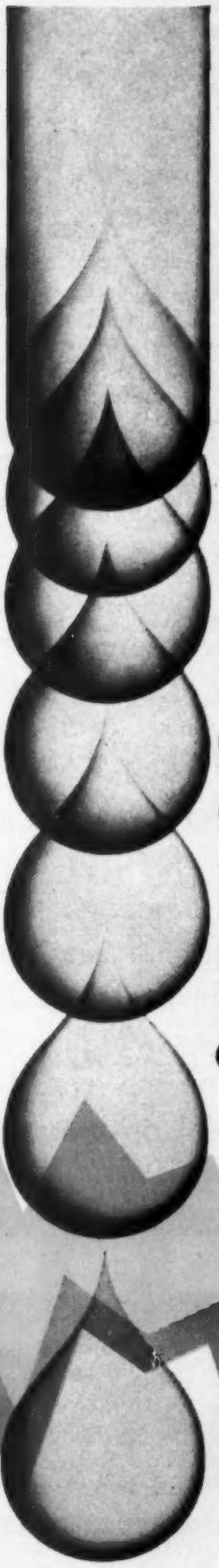
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New Hygroton® Geigy

brand of chlorthalidone

longest in action... smoothest in effect

in hypertension and edema



greater loss of sodium
lesser loss of potassium

A new antihypertensive-saluretic, Hygroton, now enables still more effective control of hypertension and edema.

more evenly sustained therapeutic response
Because it is more prolonged in action than any other diuretic,[1] Hygroton affords a smoother, more evenly sustained response.

more nearly pure natriuretic effect
Hygroton produces only minimal potassium loss . . . affords a better sodium-potassium ratio than other saluretics.[3]

more liberal diet for the patient
As a rule, with Hygroton, restriction of dietary salt is unnecessary.

more convenience and economy
For maintenance therapy three doses per week suffice to manage the vast majority of cases.[2]

in arterial hypertension
Sustained control without side reactions.

in edematous states
Copious diuresis without electrolyte imbalance.

Hygroton®, brand of chlorthalidone: White, single-scored tablets of 100 mg. in bottles of 100.

References:
(1) Stenger, E. G., et al.: Schweiz. med. Wchnschr. 89:1126, 1959. (2) Fuchs, M., Res: et al.: Current Therap. Research 2:11, January, 1960. (3) Ford, R. V.: Manuscript submitted for publication.

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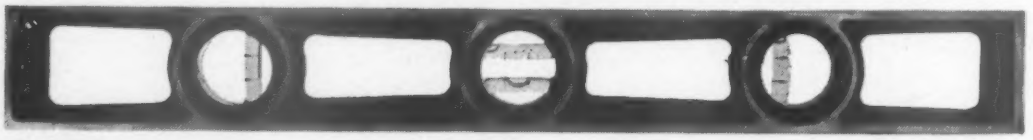
for balanced diuresis in:

cardiac edema • congestive heart failure • premenstrual tension • edema of pregnancy toxemia of pregnancy • obesity

often invaluable in: epilepsy Ménière's syndrome • glaucoma

Ample diuresis for the usual edematous patient . . . gentle . . . without excessive distortion of electrolyte or normal water patterns . . . without effect on blood pressure.

Scored tablets of 250 mg. Ampuls of 500 mg. for parenteral use.



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basic to the Art of hypertension management



moderil®
brand of rescinnamine

a refinement in rauwolfia alkaloid therapy

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IN BRIEF

MODERIL is rescinnamine, a purified rauwolfia alkaloid providing the benefits of reserpine with reduced frequency and/or severity of certain reserpine side effects. Rauwolfia has been referred to as the first agent to be tried and the last omitted in antihypertensive therapy. When **MODERIL** is given with other antihypertensive agents, the latter may often be administered in lower dosage with fewer undesired reactions.

INDICATIONS: Primary therapy in mild to moderate labile hypertension. In more severe cases, as adjunctive therapy with other agents.

ADMINISTRATION AND DOSAGE: Adjust dosage to minimum level for optimal therapeutic effect. Recommended initial dose—one 0.5 mg. tablet twice a day for two weeks. Significant side effects are unusual with **MODERIL**, but should they occur, reduce dosage to one 0.25 mg. tablet twice daily. When optimal hypotensive effects are obtained during initial period, this same reduced dosage or less may be used. If greater hypotensive effects than those observed during this period are required, cautiously increase dose by 0.25 mg. per day (up to 2.0 mg. per day) and consider combined therapy. Doses should be taken after meals to minimize possible adverse effects of increased gastric secretion.

Initial dosage for children 3-12 years of age is up to 0.25 mg. twice daily for one week. Children should be observed closely and when therapeutic effect is achieved, this dose should be reduced by half, i.e., 0.25 mg. daily.

SIDE EFFECTS: Same type as with reserpine but usually with reduced incidence or severity, e.g., mental depression, bradycardia, nightmares, and fatigue. Nasal stuffiness or congestion may occur but usually disappears with discontinuation of the drug or on use of topical vasoconstrictors or antihistamines. Increased frequency of defecation and/or looseness of stools is an occasional reaction. There have been occasional reports of serious hypotension in persons on *Rauwolfia* compounds who undergo surgery with general or spinal anesthesia. It is suggested that **MODERIL** be discontinued two weeks before surgery, when feasible, or other appropriate measures be taken.

PRECAUTIONS: Because rauwolfia preparations may increase gastric secretion, **MODERIL** should be used with caution in patients with a history of peptic ulcer.

SUPPLIED: Yellow, scored, oval tablets of 0.25 mg., bottles of 100 and 500; salmon, scored, oval tablets of 0.5 mg., bottles of 100.

More detailed professional information available on request.


another patient with hypertension?





indicated in all degrees of hypertension

effective by itself in most hypertensives

HYDROPRES*

HYDRODIURIL® with RESERPINE
(HYDROCHLOROTHIAZIDE)

HYDROPRES can be used:

- *alone* **(In most patients, HYDROPRES is the only antihypertensive medication needed.)**
- *as basic therapy, adding other drugs if necessary* **(Should other antihypertensive agents need to be added, they can be given in much lower than usual dosage so that their side effects are often strikingly reduced.)**
- *as replacement therapy, in patients now treated with other drugs*
  (In patients treated with rauwolfia or its derivatives, HYDROPRES can produce a greater antihypertensive effect. Moreover, HYDROPRES is less likely to cause side effects characteristic of rauwolfia, since the required dosage of reserpine is usually less when given in combination with HydroDIURIL than when given alone.)

HYDROPRES-25
25 mg. HydroDIURIL, 0.125 mg. reserpine.
One tablet one to four times a day.

HYDROPRES-50
50 mg. HydroDIURIL, 0.125 mg. reserpine.
One tablet one or two times a day.

If the patient is receiving ganglion blocking drugs or hydralazine, their dosage must be cut in half when HYDROPRES is added.

For additional information, write Professional Services, Merck Sharp & Dohme, West Point, Pa.

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*HYDROPRES AND HYDRODIURIL ARE TRADEMARKS OF MERCK & CO., INC.

two reliable
oral anticoagulants
adapted to
different needs

Sintrom®
brand of acenocoumarol
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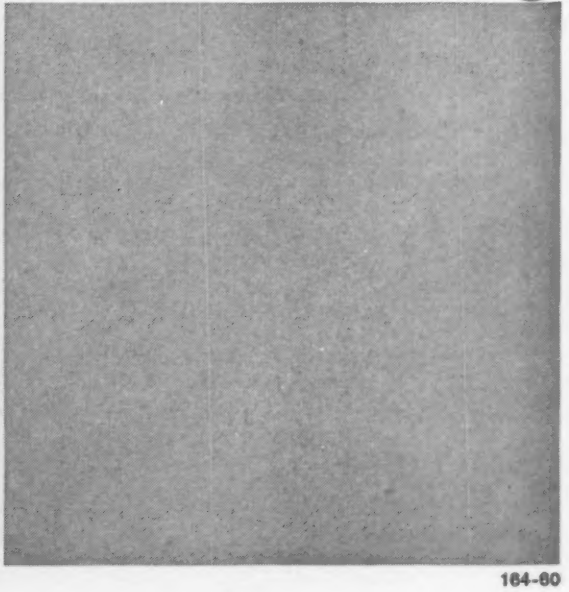
Tromexan is distinguished by rapid onset of hypoprothrombinemic effect and by an equally rapid decline. It is particularly indicated when either prompt anticoagulant effect is imperative or termination of therapy is required, as for surgical intervention.

Sintrom has a rate of action intermediate between that of Tromexan and Dicumarol.® It is noted for the ease with which a stable prothrombin response can be maintained on uniform daily dosage. Consequently it is exceptionally well adapted to long-term therapy.

Tromexan®, brand of ethyl biscoumacetate: Scored tablets of 150 mg. and 300 mg. Sintrom®, brand of acenocoumarol: Double-scored tablets of 4 mg.

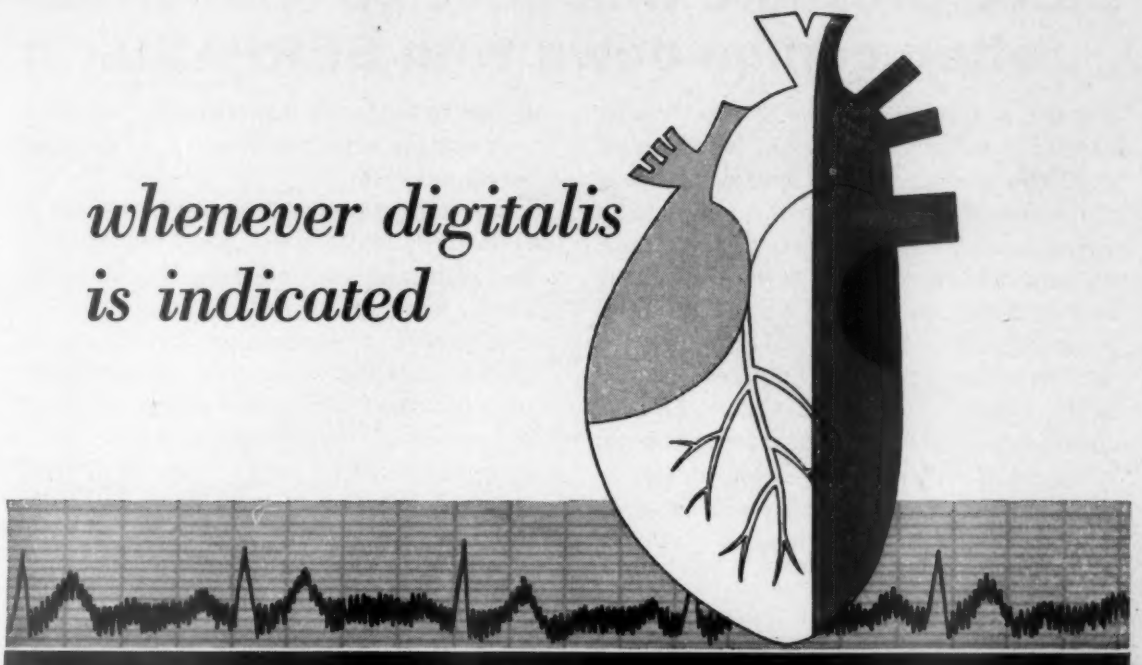
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formerly known as Digoxin 'B. W. & Co.'

"If one digitalis agent were to be recommended for its adaptability to the many and varied clinical contingencies, we believe Digoxin would be the drug of choice."

Lown, B., and Levine, S. A.: Current Concepts in Digitalis Therapy, Boston, Little, Brown & Company, 1954, p. 23, par. 2.

'LANOXIN' TABLETS	'LANOXIN' INJECTION	'LANOXIN' ELIXIR PEDIATRIC
0.25 mg. scored (white) 0.5 mg. scored (green)	0.5 mg. in 2 cc. (I.M. or I.V.)	0.05 mg. in 1 cc.

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Blood pressure that goes up with stress often comes down with SERPASIL®

(reserpine CIBA)

One reason that many cases of hypertension respond to Serpasil is that many cases are associated with stress. Stress situations produce stimuli which pass through the sympathetic nerves, constricting blood vessels, and increasing heart rate. Hyperactivity of the sympathetic nervous system may elevate blood pressure; if prolonged, this may produce frank hypertension. By blocking the flow of excessive stimuli to the sympathetic nervous system, Serpasil guards against stress-induced vasoconstriction, brings blood pressure down slowly and gently.

In mild to moderate hypertension, Serpasil is basic therapy, effective alone "... in about 70 per cent of cases..."*

In severe hypertension, Serpasil is valuable as a primer. By adjusting the patient to the physiologic setting of lower pressure, it smooths the way for more potent antihypertensives.

In all grades of hypertension, Serpasil may be used as a background agent. By permitting lower dosage of more potent antihypertensives, Serpasil minimizes the incidence and severity of their side effects.

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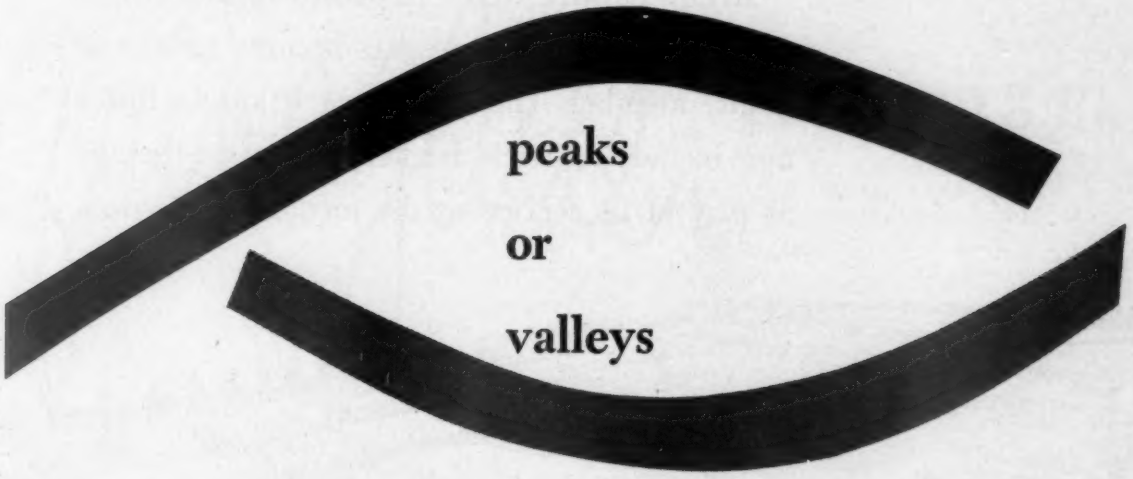
*Coan, J. P., McAlpine, J. C., and Boone, J. A.: J. South Carolina M. A. 51:417 (Dec.) 1955.

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the original crystalline digitoxin

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You will find that Digitaline Nativelle, the original crystalline digitoxin, provides exactly the balanced, controlled maintenance dose you want for your cardiac patient. Its duration of activity is neither too short nor unduly prolonged, well suited to daily maintenance therapy. Its complete absorption and purity assure uniform potency, precision of dosage, total utilization and effectiveness. A product of Nativelle, Inc.

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no let-down in plasma levels where arrhythmias tend to occur.

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1. Bellet, S., Finkelstein, D., and Gilmore, H.: A.M.A. Archives Int. Med. 100:750, 1957.
2. Bellet, S.: Amer. Heart J. 56:479, 1958.
3. Finkelstein, D.: Penn. Med. J. 61:1216, 1958.
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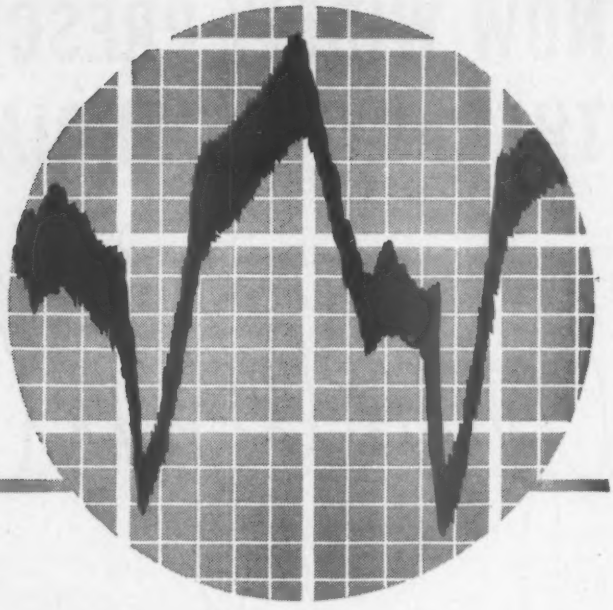
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treatment
of cardiac
arrhythmias



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Injectable Quinidine Hydrochloride, Brewer—the first injectable quinidine available in America—is especially indicated in ventricular tachycardia and in certain cases of auricular fibrillation. It usually begins to act within 15 to 30 minutes, and reaches its maximum effect in 1½ to 3 hours. In one study of 107 cases of paroxysmal ventricular tachycardia, the investigators conclude: "The treatment of choice was quinidine therapy."[1] In refractory cases of paroxysmal tachycardia, the intravenous administration of Quinidine has proved effective.[2]

ADMINISTRATION: Intramuscularly, or if necessary, intravenously.

SUPPLIED: Quinidine Hydrochloride Injectable (0.6 gm.) in 5 cc. ampuls. Quinidine Hydrochloride Injectable (0.18 gm.) in 1½ cc. ampuls. Also available for oral administration—Quindul (Quinidine Sulfate, Brewer) (3 gr.) in capsules, tablets and enteric coated tablets.

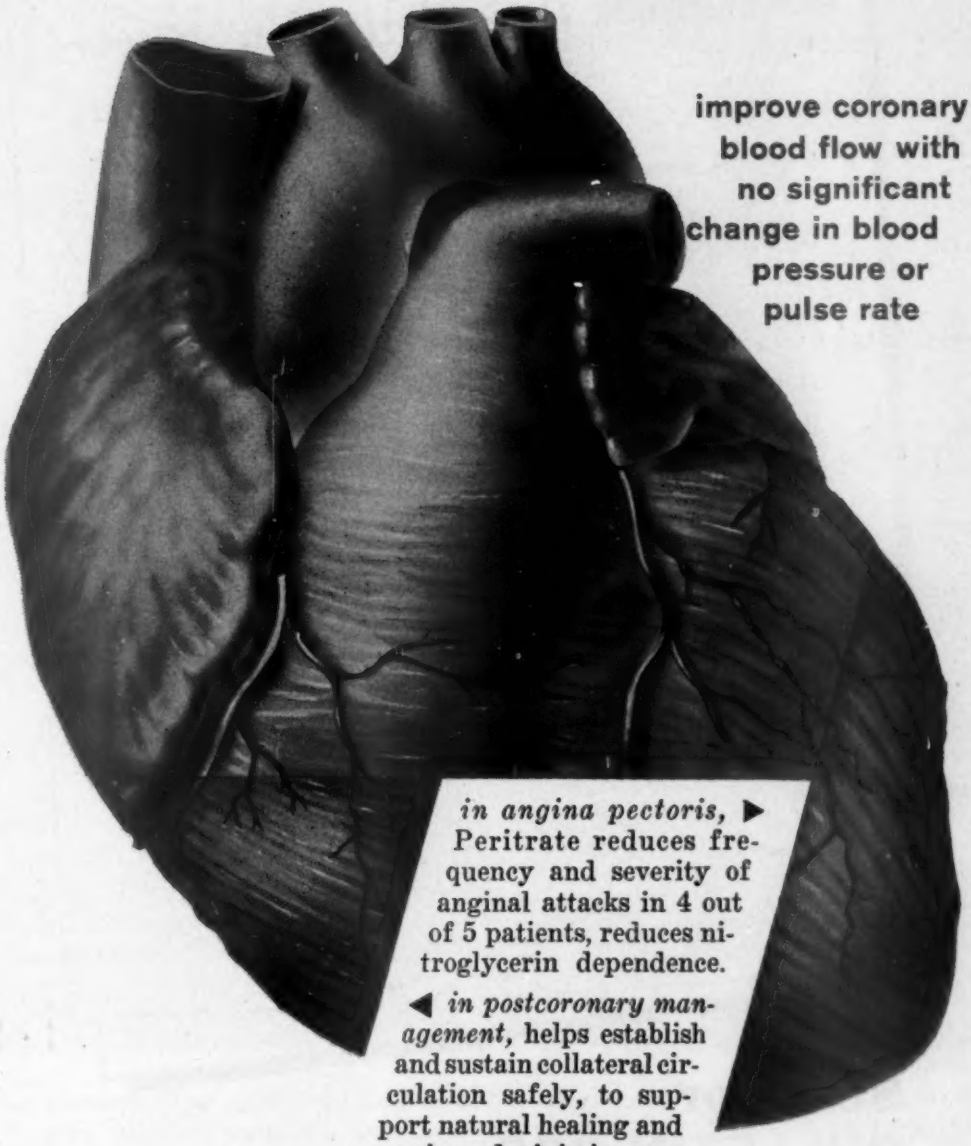
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1. Armbrust, C.A., Jr., and Levine, S.A.: Paroxysmal Ventricular Tachycardia: A Study of 107 Cases. Circulation 1:28 (1950)
2. Bell, G.D., Bradley, R.B., and Hurxthal, L.M.: Paroxysmal Tachycardia, Experiences with Massive Doses of Quinidine Intravenously in a Refractory Case. Circulation 1:939 (1950)



improve coronary blood flow with no significant change in blood pressure or pulse rate

in angina pectoris, ▶ Peritrate reduces frequency and severity of anginal attacks in 4 out of 5 patients, reduces nitroglycerin dependence.

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basic in coronary artery disease

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brand of pentaerythritol tetranitrate

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Peritrate with Phenobarbital Sustained Action

1 tablet on arising and 1 tablet 12 hours later.

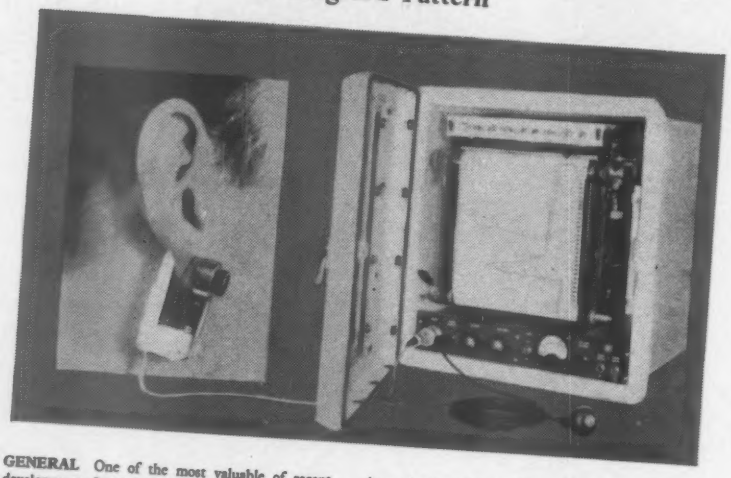
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Cambridge

Dye–Dilution Curve Recording Apparatus

Shillingford Pattern



GENERAL One of the most valuable of recent developments for the diagnosis of cardiac diseases is the Dye-Dilution Curve Recording Apparatus produced by the Cambridge Instrument Company. By its use, cardiac output can be determined and intracardiac shunts can be detected and located. It is also finding increasing use in the study of congenital heart conditions and valvular incompetence.

The Cambridge Dye-Dilution Apparatus is designed to record the change of concentration of a dye injected at selected sites in the venous circulation. This change is detected by a photo-electric attachment on the ear or by a photo-electric cuvette through which blood—from the radial artery, for example—is permitted to flow. Output from either of these units is fed into a special Cambridge Electronic Recorder which incorporates a highly sensitive and stable d.c. amplifier. The instant of dye injection is marked on the recorder chart by momentarily depressing an external push-button switch. When the dye passes through the ear or the cuvette, the recorder pen moves across the chart and a time concentration curve is traced.

EAR ATTACHMENT (Fig. 1). This unit, designed for clipping on to the lobe of the ear, gives an electrical output proportional to the concentration of the dye as it circulates through the capillaries of the ear. Photocells, mounted in one arm of the clip, form the sensitive element. On the opposing arm of the clip is mounted an easily replaceable lamp. A light flexible lead, terminating in a 6-point socket, connects the attachment to the recorder. Two interchangeable types of ear attachment can be supplied, one for use with Evans Blue Dye (Azovan Blue) and the other for Fox Cardio Green (Indocyanine Green).

Send for BULLETIN 326

THE CAMBRIDGE DYE-DILUTION CURVE RECORDING APPARATUS

Records changes of concentration of a dye injected at selected sites in the venous circulation. By its use, cardiac output can be determined and intracardiac shunts can be detected and located. It is also finding increasing use in the study of congenital heart conditions and valvular incompetence. The ear piece and the cuvette can be readily changed for use with either Fox green or Evans blue or one of the other blue dyes.

CAMBRIDGE INSTRUMENT CO., INC.

Graybar Bldg., 420 Lex. Ave., N. Y. 17, N. Y.

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PIONEER MANUFACTURERS OF THE ELECTROCARDIOGRAPH

this hypertensive patient prefers Singoserp... and so does his physician

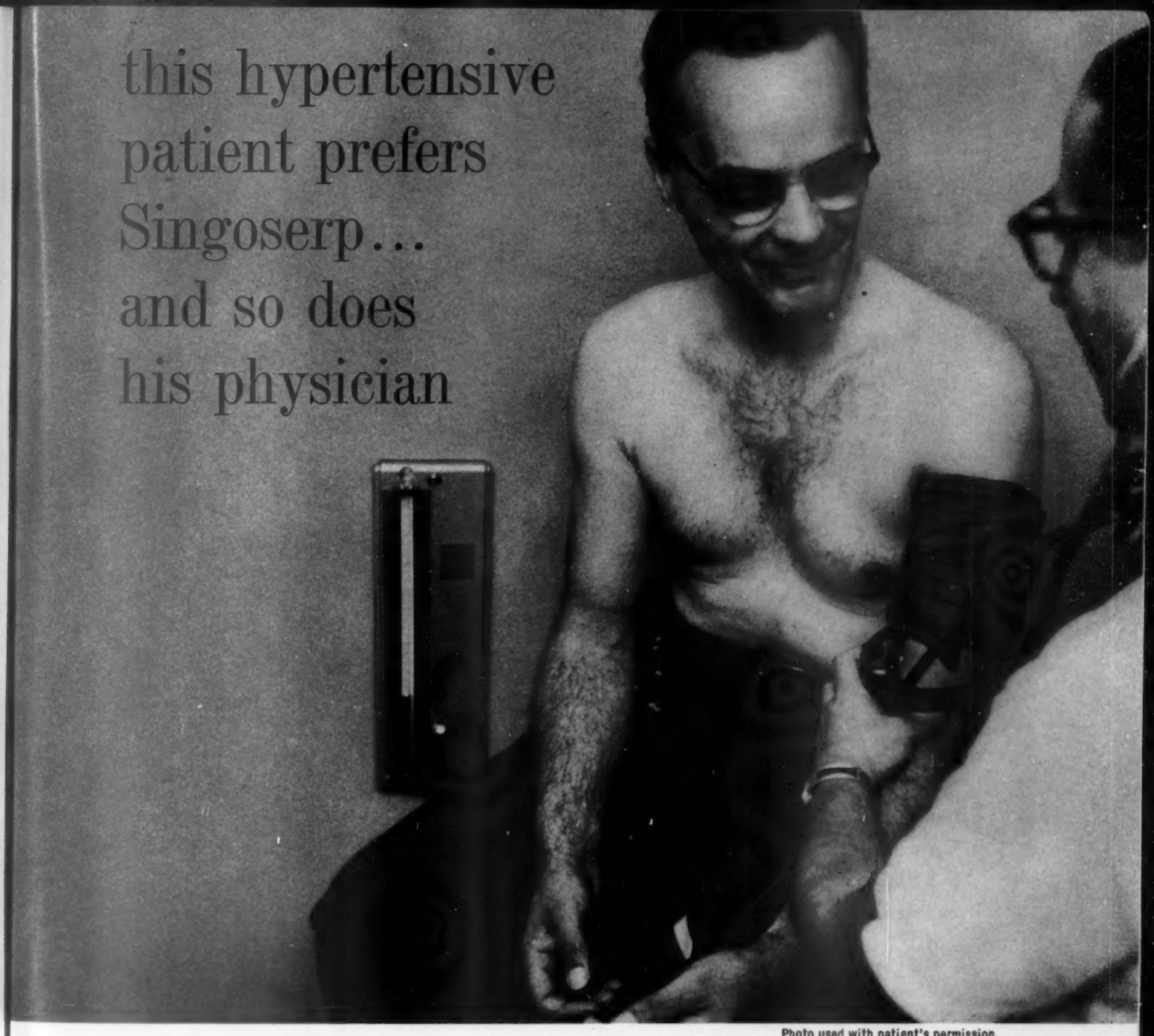


Photo used with patient's permission.

Patient's comment: "The other drug [whole root rauwolfia] made me feel lazy. I just didn't feel in the mood to make my calls. My nose used to get stuffed up, too. This new pill [Singoserp] doesn't give me any trouble at all."

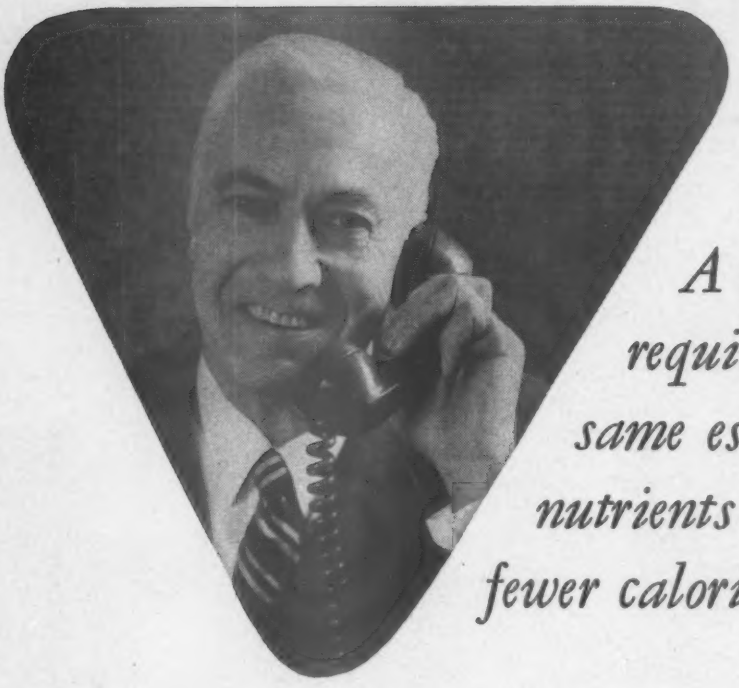
Clinician's report: J. M., a salesman, had a 16-year history of hypertension. Blood pressure at first examination was 190/100 mm. Hg. Whole root rauwolfia lowered pressure to 140/80 — but side effects were intolerable. Singoserp, 0.5 mg. daily, further reduced pressure to 130/80 and eliminated all drug symptoms.

Many hypertensive patients and their physicians prefer Singoserp® because it usually lowers blood pressure without rauwolfia side effects

SUPPLIED: Singoserp **Tablets, 1 mg. (white, scored). Also available: Singoserp®-Esidrix® Tablets #2 (white), each containing 1 mg. Singoserp and 25 mg. Esidrix; Singoserp®-Esidrix® Tablets #1 (white), each containing 0.5 mg. Singoserp and 25 mg. Esidrix. Complete information sent on request.**
Singoserp® (syrosingopine CIBA) Singoserp®-Esidrix® (syrosingopine and hydrochlorothiazide CIBA)

2/2844HB

CIBA
SUMMIT, NEW JERSEY



A man of 65 requires same essential nutrients but fewer calories

Due in part to diminished physical activities, the recommended daily dietary allowances for "Men, 65 years," are lower in calories but similar in essential nutrients recommended for younger age groups. This reduction in calories is easily accomplished by a moderate reduction in dietary fat. *A basic cereal and milk breakfast* as shown in the table below merits consideration because *its moderate low-fat content* of 10.9 gm. provides 20 per cent of the total calories, yet it provides for this age group and for most others about one-fourth of the recommended daily dietary allowances of protein, important B vitamins, and essential minerals. The Iowa Breakfast Studies on Men Past 60 Years of Age demonstrated that *a well-balanced, moderate low-fat morning meal was a sound one for the maintenance of health and well-being during the morning hours.*

Recommended Daily Dietary Allowances* and the Nutritional Contribution of a Basic Cereal and Milk Moderate Low-Fat Breakfast

Menu: Orange Juice—4 oz.;
Cereal, dry weight—1 oz.;
Whole Milk—4 oz.; Sugar—1 teaspoon;
Toast (white, enriched)—2 slices;
Butter—5 gm. (about 1 teaspoon);
Nonfat Milk—8 oz.

Nutrients	Calories	Protein	Calcium	Iron	Vitamin A	Thiamine	Riboflavin	Niacin equiv.	Ascorbic Acid
Totals supplied by Basic Breakfast	503	20.9 gm.	0.532 gm.	2.7 mg.	588 I.U.	0.46 mg.	0.80 mg.	7.36 mg.	65.5 mg.
Recommended Dietary Allowances—Men, 65 Years (70 kg.—154 lb.)	2550	70 gm.	0.8 gm.	10 mg.	5000 I.U.	1.3 mg.	1.8 mg.	18 mg.	75 mg.
Percentage Contributed by Basic Breakfast	19.7%	29.8%	66.5%	27.0%	11.8%	35.4%	44.4%	40.9%	87.3%

Cereal Institute, Inc.: Breakfast Source Book. Chicago: Cereal Institute, Inc., 1959.
Food & Nutrition Bd.: Recommended Dietary Allowances, Revised 1958. Natl. Acad. Sci.—Natl. Research Council Publication 589, 1958.
Watt, B. K., and Merrill, A. L.: Composition of Foods—Raw, Processed, Prepared. U.S.D.A. Agriculture Handbook No. 8, 1950.

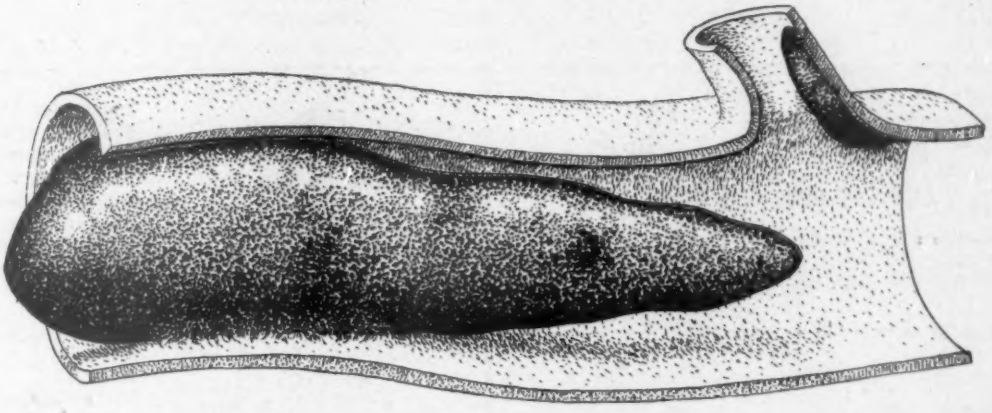
**The allowance levels are intended to cover individual variations among most normal persons as they live in the United States under usual environmental stresses. Calorie allowances apply to individuals usually engaged in moderate physical activity. For office workers or others in sedentary occupations they are excessive. Adjustments must be made for variations in body size, age, physical activity, and environmental temperature.*

CEREAL INSTITUTE, INC.
135 South La Salle Street, Chicago 3

A research and educational endeavor devoted to the betterment of national nutrition

Announcing...a new agent for lysis of

VASCULAR THROMBI



THROMBOLYSIN, supplemented by anticoagulant therapy, can greatly reduce mortality and morbidity in thrombophlebitis, phlebothrombosis, pulmonary embolism, and certain arterial thrombi.* Recently formed clots are lysed rapidly, usually in 24 hours.

to lyse thrombi

THROMBOLYSIN.®

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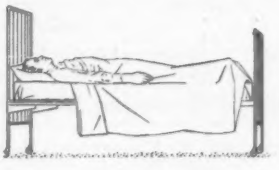
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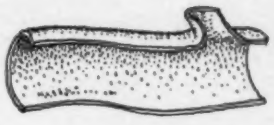
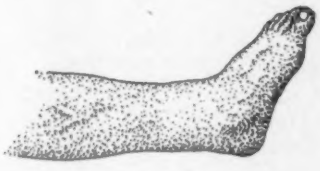
THROMBOLYSIN®

FIBRINOLYSIN, HUMAN

early use greatly reduces morbidity and mortality in thrombophlebitis, phlebothrombosis, pulmonary embolism, and certain arterial thrombi

Results of therapy	Bed rest
Effect on intravascular thrombi	 Clot may form permanent obstruction to blood flow. New clots may form.
Effect on pulmonary emboli	 Sudden death from pulmonary embolism is an ever-present hazard. One or more nonfatal pulmonary emboli may result in irreversible lung damage or secondary pneumonia.
Effect on duration of illness and convalescence	 Weeks of hospitalization or bed rest at home are commonly required in the management of thrombophlebitis, phlebothrombosis, pulmonary embolism, and arterial thrombosis.
Frequency and severity of postphlebitic syndrome	 Chronic leg swelling, severe secondary varicose veins, and leg ulcers are common sequelae.



Anticoagulant + Bed rest		THROMBOLYSIN + Anticoagulant + Bed rest	
	Anticoagulants cannot remove formed clot. However, they help prevent its extension and minimize formation of new clots.		Recently formed intravascular clots are lysed and the formation of new clots is inhibited. Circulation is restored and maintained, with rapid symptomatic relief.
	The careful use of anticoagulants reduces the occurrence of pulmonary emboli.		The incidence and severity of pulmonary emboli are greatly reduced since THROMBOLYSIN acts to remove thrombi before they can become emboli.
	Thromboembolic illness and convalescence are shortened.		A striking reduction is observed in the duration of hospital stay, bed rest, and convalescence.
	The incidence and severity of the postphlebitic syndrome are reduced.		Postphlebitic complications are prevented or greatly minimized.



What is THROMBOLYSIN?

THROMBOLYSIN is Fibrinolysin, Human. It is prepared by activating the profibrinolysin-rich Fraction III – 3 of pooled human plasma with highly-purified streptokinase and then lyophilizing it. THROMBOLYSIN helps restore the natural equilibrium between clot formation and clot lysis, thereby enhancing the ability of the blood to maintain normal flow.

In What Conditions is it Indicated?

THROMBOLYSIN is indicated in thrombophlebitis, phlebothrombosis, pulmonary embolism, and certain arterial thrombi.

*(NOTE: *Successful lysis of thrombi of major cerebral vessels has been reported. However, additional experience is required to define the indications and contraindications of therapy in such patients. THROMBOLYSIN has also been administered to patients with acute myocardial infarction, but the scope of this work is still too limited to permit conclusions about its safety or benefit.*)

When Should Therapy be Initiated?

Treatment with THROMBOLYSIN should be started as soon as possible after a thrombus has formed. Blood clots begin to organize shortly after formation and may become encased in a layer of endothelial cells, making them resistant to the action of THROMBOLYSIN. Usually, more rapid lysis can be expected to take place when treatment is initiated within five days after a thrombus has formed; however, in some cases successful lysis has been accomplished when treatment was not initiated for several weeks after thrombus formation.

Can THROMBOLYSIN be Given to Patients Being Treated with Anticoagulants?

Yes. Patients who have been on anticoagulant therapy can be expected to improve when THROMBOLYSIN is added to their program of treatment.

Does THROMBOLYSIN Increase the Incidence of Embolism?

Clinical studies indicate that it does not. In fact, if any evidence of embolization should appear, it is important to continue THROMBOLYSIN until symptoms have disappeared.

What is the Dosage?

The dosage most frequently used by investigators has been 4 vials (200,000 MSD units) per day by intravenous infusion. This is usually administered by giving 1 vial per hour for 4 consecutive hours. Alternatively, 1 vial (50,000 MSD units) per hour may be given for 2 consecutive hours and repeated in 3 to 6 hours. The dosage range is 1 vial (50,000 MSD units) to 2 vials (100,000 MSD units) an hour by intravenous drip, for 1 to 6 hours, depending on the nature of the clot and the response

Vascular thrombi
can now be
treated rapidly
by a new agent

THRO

For additional information, see package circular or write to Professional Services, Merck Sharp & Dohme, West Point, Pa.



of the patient. Most patients respond in one day; those who do not may require additional doses for three or four successive days.

Patients not under active treatment with anticoagulants at the time of the thromboembolic episode:

New clot formation is unlikely to occur during the administration of THROMBOLYSIN, so that anticoagulants may be unnecessary in this period. However, the fibrinolytic activity of THROMBOLYSIN persists only 3 to 4 hours after cessation of infusion; in patients subject to thrombosis, provision should be made to provide adequate therapeutic anticoagulant effect at this time.

Patients under active treatment with anticoagulants:

Within recommended dosages, THROMBOLYSIN produces only minor alterations in the clotting mechanism: the prothrombin time is generally increased by only a few seconds, the Lee-White clotting time by only 1 to 4 minutes, and the fibrinogen levels generally decrease by about 30 percent of control values. In themselves, these alterations are probably of no clinical significance. In patients on concurrent anticoagulant therapy in whom the clotting mechanism is depressed to midtherapeutic levels, the small additional depression due to THROMBOLYSIN should produce no added danger; however, the addition of THROMBOLYSIN may be hazardous when the therapeutic anticoagulant level already threatens to exceed safe limits.

What Other Precautions are Necessary?

THROMBOLYSIN is contraindicated in the presence of a hemorrhagic diathesis or hypofibrinogenemia. Fibrinolytic activity usually increases spontaneously for a short period after anesthesia or surgery. Therefore, THROMBOLYSIN should be used with caution because lysis of the clots at the operative site may occur.

Bleeding from open wounds or recent operative sites can occur during therapy. Usually this has been observed only in patients receiving both an anticoagulant and THROMBOLYSIN. In such cases, the bleeding was controlled by the use of plasma or whole blood transfusions. A specific antagonist to the anticoagulant may also be used.

What Side Effects May Occur?

Febrile reactions may occur, but these are rarely severe. When they do occur, the temperature usually rises rapidly to a peak, then returns to normal within 24 hours. In some patients, a rise in temperature above 1.5 to 2 degrees F. is accompanied by chills, nausea, vomiting, dizziness, headache, muscle pain, back pain, tachycardia, or hypotension.

How is it Supplied? 100-cc. vials containing 50,000 MSD units.

to lyse thrombi

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MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., WEST POINT, PA.

THROMBOLYSIN IS A TRADEMARK OF MERCK & CO., INC.





Cardiovascular patients respond in a few days. Thanks to your prompt treatment and the smooth action of Deprol, his depression is relieved and his anxiety calmed – *often in two or three days.* He eats well, sleeps well and his depression no longer complicates your basic regimen.

Lifts depression...as it calms anxiety!

For cardiovascular patients–a smooth, balanced action that lifts depression as it calms anxiety...rapidly and safely

Balances the mood–no "seesaw" effect of amphetamine-barbiturates and energizers. While amphetamines and energizers may stimulate the patient – *they often aggravate anxiety and tension.* And although amphetamine-barbiturate combinations may counteract excessive stimulation – *they often deepen depression.*

In contrast to such "seesaw" effects, Deprol lifts depression as it calms anxiety – both at the same time.

Acts swiftly–the patient often feels better, sleeps better, within two or three days. Unlike most other antidepressant drugs, Deprol relieves the patient quickly – often within two or three days.

Acts safely – no danger of hypotension. Deprol does not cause hypotension, tachycardia, jitteriness, or liver toxicity. It can be safely administered with basic cardiovascular therapy.

Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this may be gradually increased up to 3 tablets q.i.d.
Composition: 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.
Supplied: Bottles of 50 light-pink, scored tablets. Write for literature and samples.

▲Deprol▲

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Cranbury, N. J.

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safe and practical treatment of the postcoronary patient

A basic characteristic of the postcoronary patient, whether or not cholesterol levels are elevated, is his inability to clear fat from his blood stream as rapidly as the normal subject.[1-3] *Figure #1* graphically illustrates this difference in fat-clearing time by comparing atherosclerotic and normal subjects after a fat meal.[3]

"Slow clearers" gradually accumulate an excess of fat in the blood stream over a period of years as each meal adds an additional burden to an already fat-laden serum. As shown in *figure #2,* the blood literally becomes saturated with large fat particles, presenting a dual hazard to the atherosclerotic patient: the long-term danger of deposition of these fats on the vessel walls,[4] and the more immediate risk of high blood fat levels after a particularly heavy meal possibly precipitating acute coronary embarrassment.[5]

In *figure #3,* the test tube at the left contains lipemic serum, while the one at the right contains clear, or normal serum. If serum examined after a 12-hour fasting period presents a milky appearance, this is a strong indication that the patient clears fat slowly and is a candidate for antilipemic therapy in an effort to check a potentially serious situation.

'Clarin', which is heparin in the form of a *sublingual tablet,* has been demonstrated to clear lipemic serum.[2,6,7] Furthermore, a two-year study using matched controls resulted in a statistically significant reduction of recurrent myocardial infarction in 130 patients treated with 'Clarin'.[8]

'Clarin' therapy is simple and safe, requiring no clotting-time or prothrombin determinations. Complete literature is available to physicians upon request.

References: **1.** Anfinsen, C. B.: Symposium on Atherosclerosis, National Academy of Sciences, National Research Council Publication 338, 1955, p. 218. **2.** Berkowitz, D.; Likoff, W., and Spitzer, J. J.: Clin. Res. *7*:225 (Apr.) 1959. **3.** Stutman, L. J., and George, M.: Clin. Res. *7*:225 (Apr.) 1959. **4.** Wilkinson, C. F., Jr.: Annals of Int. Med. *45*:674 (Oct.) 1956. **5.** Kuo, P. T., and Joyner, C. R., Jr.: J.A.M.A. *163*:727 (March 2) 1957. **6.** Fuller, H. L.: Angiology 9:311 (Oct.) 1958. **7.** Shaftel, H. E., and Selman, D.: Angiology *10*:131 (June) 1959. **8.** Fuller, H. L.: Circulation *20*:699 (Oct.) 1959.

Clarin*

(sublingual heparin potassium, Leeming)

Fig. 1

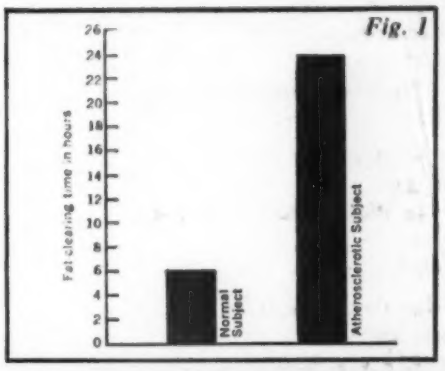


Fig. 2

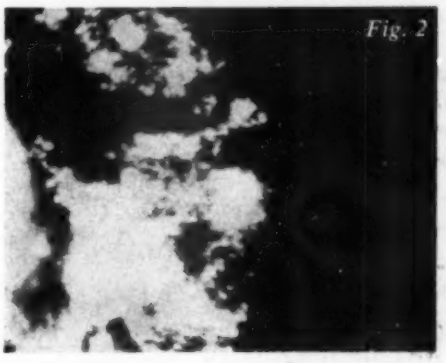
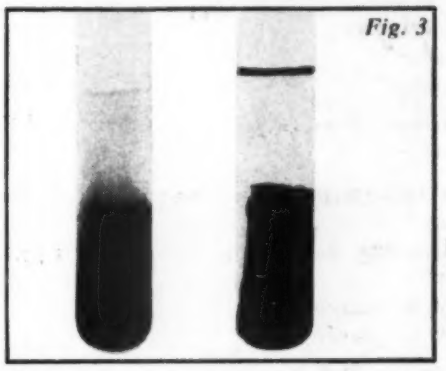


Fig. 3



Indication: For the management of hyperlipemia associated with atherosclerosis, especially in the postcoronary patient.

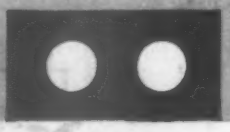
Dosage: After each meal, hold one tablet under the tongue until dissolved.

Supplied: 'Clarin' is supplied in bottles of 50 pink, sublingual tablets, each containing 1500 I.U. of heparin potassium.

*Registered trade mark. Patent applied for.

Thos. Leeming & Co., Inc.
New York 17, N. Y.

DEC 28 1959 MAR 2 8 1960
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DEC 23 1960
SEP 14 1962
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